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A G E N D A

A G E N D A (Continued)

P R O C E E D I N G S

(8:30 a.m.)

CHAIRMAN GENCO: Good morning. I'd like to welcome you all to this meeting of the Dental Plaque Subcommittee. We are going to have, as you know, a three-day meeting, and it's going to be pretty busy, and I'm sure that it will be an excellent meeting and productive.

I'd like to ask those at the table to introduce themselves so that we all are refreshed in our memory as to who is here and why they are here. Lew?

MR. CANCRO: Lew Cancro, I.L.R.

DR. ALTMAN: Don Altman, Dental Director, Arizona Department of Health, Consumer Rep.

DR. D'AGOSTINO: Ralph D'Agostino, also from the NonPrescription Drugs Advisory Committee.

DR. WU: Christine Wu, University of Illinois - Chicago, Periodontics.

DR. SAXE: Stanley Saxe, Emeritus Professor of Periodontics and Geriatric Dentistry at the University of Kentucky.

DR. BOWEN: Bill Bowen, University of

Rochester.

MS. STOVER: Rhonda Stover, FDA.

CHAIRMAN GENCO: I'm Bob Genco, State University of New York at Buffalo. I'm a periodontist and an oral biologist.

DR. McGUIRE-RIGGS: Sheila Riggs, from Iowa, an oral epidemiologist.

DR. LISTGARTEN: Max Listgarten, University of Pennsylvania, in Periodontics.

DR. SAVITT: Gene Savitt, Forsythe Dental Center, Department of Periodontics.

DR. SHERMAN: Bob Sherman, Division of OTC Drug Products, Liaison to the Subcommittee.

MS. KATZ: Linda Katz, Deputy Director, OTC Drug Products.

DR. HYMAN: Fred Hyman, Dental Officer, Division of Dermatologic and Dental Drugs, FDA.

CHAIRMAN GENCO: Thank you all. I would now like to introduce Rhonda Stover, who is the Acting Executive Secretary of the NonPrescription Drugs Advisory Committee and is acting as our Executive Secretary. Rhonda.

MS. STOVER: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

For the next several years, the Subcommittee will review information on ingredients contained in products bearing anti-plaque and anti-plaque related claims to determine whether these products are safe and effective and not misbranded for their label use.

The issues to be discussed by the Subcommittee will not have a unique impact on any particular firm or product, but rather may have widespread implications with respect to an entire class of products. In accordance with 18 United States Code 28(b), waivers have been granted to each member and consultant to participate in Subcommittee meetings.

A copy of these waiver statements may be obtained from the Agency's Freedom of Information Office, Room 12A30, Parklawn Building. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of

the need to exclude themselves from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIRMAN GENCO: Thank you. Anybody wish to make a comment?

(No response.)

Okay. Let's proceed now with the Open Public Hearing. Jerry Douglas, Dr. Douglas, from Prevention Laboratories, will talk about the efficacy of prevention mouthrinse. Dr. Douglas.

DR. DOUGLAS: Thank you, distinguished members of the panel, and ladies and gentlemen.

I am a practicing dentist, been in practice for 30 years, started working on the ingredients of prevention mouthrinse six, seven years ago. And what precipitated me to start working on the ingredients is this statement right here, that what is needed in dentistry is a treatment strategy which takes into account the uniqueness of dental decay and periodontal

disease as bacterial infections. I think we all realize that the problems in the oral cavity are related to the bacterial environment that's in that oral cavity and the disease process as a result of that.

Then when I read what Dr. Philip Marsh had to say, "control plaque qualitatively, not quantitatively", this to me fit with the first slide. We don't want to disturb the normal flora, but we want to control the pathogens.

And this fit right in with the first two slides. The bacterial oral environment differs from patient-to-patient and area-to-area in the mouth, and you all know there's many factors that affect that.

There can be different bacterial patterns in the same mouth, and I think you all are aware of that also. So, in my opinion, anything used in the oral cavity to help control plaque and gingivitis, it should be as bacterial-selective as possible, don't disturb the normal flora but try to control the pathogens.

Prevention mouthrinse. So far with the data we've collected, and we are continuing to collect data, we have two ADA clinicals in progress right now. Due to

research that was started as far back as 1973 and as current as 1989, most of it done in the Scandinavian countries, zinc shows the ability to attach to the oral tissues with anamnestic properties. In other words, be there, hang around, be able to shut down any logical factor of the pathogens as they come along.

Bacterial-selective. That goes back to the first three slides that we saw -- can we control the pathogens and at the same time do not disturb the normal flora, work to balance the oral flora -- in other words, control the "bad" guys, don't disturb the "good" guys.

Promote healing. I think this is very, very important, and that's the reason that we did the two tissue toxicity studies, to see what kind of effect our ingredients are going to have on ulcerated tissue or diseased tissue.

No staining. There's a lot of theory and thought why we have staining. A lot of it is do we cause a bacterial imbalance over a prolonged period of time. Do not alter the taste. No side effects with long-term use -- in other words, is it extremely safe. Is it safe for long-term use, and is it environmentally

compatible.

Easy to use. And we all know that compliance is a big factor. If you don't have compliance, none of us are going to be successful.

Zinc chloride and the things that you see on this slide, we stand by this simply because of the references -- and I'll be happy if anybody wants a copy of these references where you can document -- zinc does attach to the cells, extracellular and intracellular. And when this happens, it really metabolically screws that cell up. It will bloc the production of the magnesium ion which is crucial for reproduction. It interferes with the ATP or the energy process. It attacks the cycloskeletal system. You can go on and on and on. And all the way from 1973 to 1989 it really impressed me, the research that was done, and the published articles in reference to what you see on this slide.

So, in my opinion, zinc chloride is one of the most effective antimicrobials to meet perfect criteria, in my opinion, for use in the oral cavity to control or rebalance the bacterial environment.

Sodium citrate. I found this to be real interesting and, as I was selecting the ingredients for this product, I reviewed hundreds and hundreds and hundreds of published articles. We all know sodium citrate is an anticoagulant, that's very evident, but work that was done at the University of Colorado showed that sodium citrate has the ability, when complexed with the heavy metal ions, to have an effect on the inflammatory process.

I found this to be real interesting, and the way that happens, or the way they think that it happens, by shutting down is the production of enzymes or the polymorphic nucleolukocytes, which is what initiates the inflammatory process.

Sodium oral sulfate. I found this also to be very interesting, the research that was done back in the '70s and '80s in the Scandinavian countries, especially when it was incorporated with a heavy metal ion. And you all know that it's in most of the oral care products -- toothpaste -- it's used in a lot of things. And when you mix it with the heavy metal ions, it's interesting the effect that it has on that cell wall. You can take

and have a patient to rinse with a zinc chloride or a zinc rinse, mix sodium lauryl sulfate with it and have them to rinse, there will be three to five times as many cells affected. I found that to be real, real interesting.

Also, the way it competes with and attaches to the hydroxyapatite on enamel. There's a lot thought and theory that it has a tendency to be attracted to the hydroxy apatite and put a film on enamel which helps prevent plaque from attaching. A lot of research has been done on this that I think is quite interesting.

We have seen trace and trends of prevention having a softening effect on calculus -- now I didn't say remove calculus, but I said softened it to a certain extent. We think this is possible, and it's documented to a certain extent by Dr. Nukrege's (phonetic) work. EDTA sodium, which is a chelating agent and the reason it was in our formula, also removes salts from hard chemicals. In other words, if you take the salts from the calcium and the phosphorouses and calculus, which is the biggest percentage of calculus, then it's going to make it softer to a certain extent.

Hydrogen peroxide -- and there's no sense, in my opinion -- is the second line of defense in the oral cavity behind saliva, and I think the panel has already acted on hydrogen peroxide, so we're not going to spend any time on that. The slide is pretty self-explanatory.

This slide was taken just recently on a 39-year-old male who has a bacterial imbalance, really has to work at trying to keep the oral cavity healthy. He came to our practice and we put him on the rinse. He came back in three months because we wanted to see if we were making or taking the right track in trying to treat him and help him turn the bacterial population around. I think the slide is obvious to all of you. And in three months when he came back, you can see the difference. So this is quite impressive. I mean, it impressed the hygienist, me, and everybody else and even the patient, but we started asking him, did you change dentifrices, did you change toothpaste, did you use any type of oral irrigation, interproximal stimulators. Have you had a change in your diet, you know, every question we could ask him, and he says, no, I've done nothing different. And this guy is a highly educated

individual. He said, I've done nothing different since I was here three months ago.

Well, I think these two slides show us that our work is really cut out for us in prevention, that we must continue to do the research that we're doing, and continue to do new research and, if we can see trends like this, then maybe we're on the right track to doing what our goal was initially, and that is to come up with products that help rebalance the microbiological or the oral environment. Thank you.

CHAIRMAN GENCO: Are there any questions or comments of Dr. Douglas? Lew?

MR. CANCRO: Dr. Douglas, your submission involves several ingredients. Some of the characterization that you put up on your slide suggests some of those ingredients function in a cosmetic manner as opposed to a therapeutic manner, such as the softening of calculus, et cetera. And I was just wondering, in your submission -- and I'm not familiar with it, but -- have you identified what you believe to be the active ingredients are as opposed to what I see you display a combination of active ingredients plus

ingredients intended for some cosmetic benefit? That's the point of clarification I'd like you to make.

DR. DOUGLAS: I think that each one of these ingredients has merit on its own, but to do what we've set out to try to accomplish, and that is to rebalance the oral flora, control the pathogens, don't disturb the normal guys, that it is the synergies of the four ingredients that we put on the slide, the way they work together.

CHAIRMAN GENCO: Bill?

DR. BOWEN: You mentioned that you have EDTA in there to soften calculus. Won't the EDTA also soften enamel? There are at least two studies that I'm aware of in rats where the exposure to EDTA actually promoted caries.

DR. DOUGLAS: And that's a very good question and a valid question. Yes, in high concentrations, much higher than what we have in our formula, it will soften enamel, most definitely. I think Dr. Nukrege's study clarifies that very, very clearly. It's in the low concentrations in synergies with the ingredients that we have.

CHAIRMAN GENCO: Further comments, questions?

(No response.)

Thank you very much, Dr. Douglas.

We will now hear from Dr. David Drake, from the University of Iowa, and he'll talk about microbiological studies on prevention mouthrinse.

DR. DRAKE: Mr. Chairman, ladies and gentlemen, good morning. My name is David Drake, and I'm an Associate Professor of Microbiology in the Dow's Institute for Dental Research, in the College of Dentistry at the University of Iowa. I've been asked by Dr. Douglas and Prevention Laboratories to present some of the information from studies that we have conducted over the years for Prevention Laboratories.

What I'm going to talk about are some laboratory studies, standard MIC/MBC analyses we did five years ago, just to get a sense of the antimicrobial activity of these rinses; kinetics of bacteriocidal activity, looking at the rate of kill upon constant exposure over time; and then these two here are short-term exposure assays and glycolysis inhibition assays. What we do here is take standardized suspensions of

cells, briefly expose them to the rinse -- 30 seconds up to five minutes -- and then immediately dilute those organisms into -- 100 to 1,000 fold into a neutralizing broth to kind of get an idea of how organisms in the oral cavity would react to exposure to these compounds. And then a little bit about some clinical trials that were conducted in our Center for Clinical Studies at the College of Dentistry, University of Iowa -- six-month clinical trial with prevention mouthrinse -- and, obviously, I'll be focusing in the microbiological aspects, not so much the clinical -- and then also a six-month clinical trial with orthodontic rinse. There are three rinses that the company prepares. One is a standard prevention mouthrinse, there is an orthodontic-strength rinse, and then a periodontal-strength rinse, just for clarification purposes.

Most of the laboratory data has already been published. It was in the American Journal of Dentistry in 1993 so, just briefly here, MIC/MBC analyses show that if you do it in a mouthrinse 16-128 fold, that was the range, so they got really high activity against a whole spectrum of bacteria. The anaerobes were more in

the 128-fold range, and organisms, the facultatives and the yeast and so forth are more on this end of the spectrum.

Bacteriocidal connect assays show very rapid killing of all the organisms tested, which wasn't any big surprise with hydrogen peroxide. And then, interestingly, what we did with the short-term exposure assays and we found that growth of streptococcus mutans, the primary etiological agent of caries, could be inhibited on a single up to five minute exposure. And a key thing about this assay, as you can see here, first of all, this was with eight-fold diluted rinse, and at this concentration we did not see changes in the numbers of viable cells. So we're not looking at differences here in growth profiles just because the rinse killed a number of bacteria in the suspension, so the numbers of organisms here are the same. This is just looking at absorbance, a way of measuring bacterial growth over time. You can see the control cultures here grew very rapidly. They were exposed up to five minutes to distilled water. And the key thing here is that in cells exposed to prevention mouthrinse there was a

significant delay in growth and in by about 20 hours they caught back up. And this has been reproduced. We've done this a number of times. This is showing some of the best data we have.

But, again, we also have numbers here, instead of just adsorbents, if you have the numbers of bacteria, we see the same kind of thing, concentrations are the same at the beginning, and then they slowly grow up with prevention in the control cells.

Associated with that, if you look at acid production just by looking at changes of pH over time, control cells we see a pH drop as seen here, cells exposed to 30 seconds to up to five minutes with prevention mouthrinse, you can see at the four hour time point that the control cells are already dropped below a pH of 6 where cells exposed to the prevention mouthrinse were still around neutrality.

We did not have time points in here, so obviously this line is drawn this way. I don't have a good sense of how long this stayed at neutrality before it did drop eventually down by eight hours. So, I found this kind of interesting in that exposure to a rinse at

a dilution did not kill the cells, still has an impact on the physiology of the organisms, are not able to grow as well at all so, as a result of that, they don't produce a lot of acid.

This was a recent study we did with organisms using the periodontal rinse. And we grew up each one of these organisms here -- actinomyces viscosis, petro streptococcus micros, P. gingivitis, and fusobacteria nucleatum individually, and then we created mixed suspensions because, obviously, the organisms are not by themselves in the oral cavity, they exist in a community environment, and then exposed them to the periodontal rinse for 30 seconds, and then immediately diluted those samples into a neutralizing broth. Control suspensions were exposed to distilled water. You can see those organisms basically do just fine. We started off anywhere from 10-6 to 10-7 cell concentration, and we compared prevention with peridex 0.12 percent chlorhexidine digluconate, and three out of four organisms no difference between the two rinses. Actually, it's kind of interesting that actinomyces survives this mixed culture type of exposure basically

no differently between the control and these two rinses.

Clinical trials. We did a six-month double-blind randomized study with 62 subjects. We looked at plaque indices at baseline, six weeks, three months, and six months, and then we looked at a lot of aspects of the oral microflora. These patients were all given prophase at the beginning of the study, they had everybody at the same level. And then two weeks past the prophase, then we did the baseline measurements, and then, of course, went through. This is with the normal prevention mouthrinse. The oral microflora, again, baseline, six weeks, three months, six months. We looked at total aerobic and anaerobic flora. We looked at plaque pigment in bacteroides total subcounts here. And we also did see some of those, total actinomyces, total streptococci, and also mutan streptococci within the total streptococci, looking for the appearance of opportunists -- obviously, you don't want to have a rinse that's going to select organisms you don't want to have there in the first place -- staphylococci, enterics, and yeast.

The other thing that we did here was look at

potential development of resistance, and so we took representative samples from all of these organisms at baseline and all the time points, and then conducted the MIC/MBC analyses to see whether or not over time we saw development of any kind of resistance pattern.

We also did banohydrolysis assays in here, as described by Walter Losch (phonetic), and we looked at basic forms of microorganisms through phase contrast microscopy.

Briefly, I'm going to show you some of the slides real quick, just looking at some of the data. This is looking at log counts per ml of the reduced transport media, and then the placebo rinse was in the red and the active rinse is always in the green. The streptococcus mutans we really didn't see any change in numbers. You'll notice these numbers are low to begin with. These are healthy patients, they are not caries active, so these are actually fairly, but there was really no significant change over time.

Lactobacilli, we hardly ever isolated these organisms from the plaque of these patients. These were pooled plaque samples from the four first molar teeth,

by the way, and there are very, very low numbers as you can see here, but there was really no change over time for the lactobacilli.

The staphylococci -- the one thing we did notice and I participated in the discussions with my clinical colleagues, in terms of compliance, there were some compliance issues, some problems we had, at the six-month time point. And we had evidence from that from diary cards the patients had written down comments like "I'm getting tired of this study", "I'm not being paid enough", things like that. And also we had the rinse bottles returned at each time point and weighed those, and we saw that there were some patients were not on both sides, placebo and active, that were no longer -- this is a long span of time from three months to six months, I think it plagues any type of clinical trial you do --- but we did see trends in some of these, and at the end of six months it looked like both groups got worse, and we think a lot of that had to do with the compliance.

For the total staphylococci, again, very low numbers, but you can see a trend here. This came close

to statistical significance, p-values of .08, .09, that range, that didn't quite make significance, but there was definitely a trend. It looked like here that the active rinse had slightly lower numbers.

Looking at enterics, we specied some of these, but again very low. Of the total numbers here, you can see with the placebo group there's a general rise whereas the active rinse is actually a slight decrease. This actually was not statistically significant, but the p-value was .07 so, again, another right at the borderline of that arbitrary value of .05.

Candida albicans, the same kind of thing. Looking at numbers very low isolation from these patients, no real difference over a three-month period of time. Some of these organisms, if you look at them in terms of proportions of organisms within the total cultible (phonetic) flora, you would actually see some difference. Again, it didn't reach statistical significance, but I decided just to show you the actual numbers.

One of the black plaque prevotella intermedia show again baseline counts, and over time you can see a

rise here at six months, but again there really was no statistically significant difference between these organisms over time in these groups over time.

We also did a clinical trial with the orthodontic rinse, and this was a six-month trial, 42 subjects undergoing, as my clinical colleagues called it, "comprehensive orthodontic treatment". Plaque gingival and a new plaque index that they created called a bracket-plaque index, and then oral microflora, again total aerobic-anaerobic flora, t.streptococci, mutan streptococci, and lactobacilli. These patients were obviously much younger, 8 to 18 year range.

I was going to show you one slide, and what I'm showing here is percent of total cultible flora for strep mutans. It turned out that compliance in this study was great. These kids participated real well. We didn't see any sense of a problem, but what we did find by the six-month time point, if you look in terms of percent flora in the placebo group, it's pretty high, and this is not unusual in orthodontic patients when you have these kinds of plaque accumulations around the brackets and so forth. And it was fairly high in terms

of the total cultible flora, but the active rinse was actually quite low. And this one right here was statistically significantly different between the active -- at that point in time, the active and the placebo rinse.

So, a summary of what we've done -- laboratory studies, prevention mouthrinse exhibits a very strong bacteriocidal activity against a spectrum of microorganisms associated with oral diseases. This is all laboratory based. Brief exposure of suspensions of strep mutans to dilutions of prevention mouthrinse that do not kill the cells causes inhibition of growth and acid production.

The clinical studies. A key thing we did find is that use of prevention mouthrinse over a six-month period did not select for opportunistic pathogens within the supragingival plaque community study. Use of the orthodontic rinse resulted in mutans streptococci becoming less dominant at the six-month time point. Thank you.

CHAIRMAN GENCO: Thank you, Dr. Drake. Any questions from the panel? Chris?

DR. WU: Is there a reason why you selected normal healthy patients for the clinical study?

DR. DRAKE: The prevention mouthrinse has always been touted as something that controls flora and regular prevention is not necessarily for treatment, so we started the first clinical study to see how it affects the flora in normal patients and to address the issue of whether or not you see the appearance of opportunists, which is obviously a major thing. So that's why -- I think it's critical that down the line that there should be studies with the periorinse and so forth with diseased patients.

CHAIRMAN GENCO: Bill, and then Max.

DR. BOWEN: David, I noticed that in your in vitro studies, that actinomyces viscosis seem to be comparatively resistant to the effects. Based on that, I would have anticipated perhaps an overgrowth in the clinical studies, but I didn't see any data on the actinomyces in the clinical studies. Were those conducted?

DR. DRAKE: Yes, those were conducted. I didn't show all the data, obviously. There was no

change in total actinomyces between the control and active groups through the time. Those short-term exposure assays with that mixed culture was intriguing, that the actinomyces wasn't changed. It turns out that actinomyces by itself is highly susceptible. So if one was in that mixed culture environment for whatever reason, it was not touched, and that always intrigues me in terms of microbial ecology.

CHAIRMAN GENCO: Dr. Listgarten.

DR. LISTGARTEN: The perio and the ortho version of the rinse have about two and a half to three times the strength, the concentration of active ingredients, than the regular rinse, and I wonder if the test results that you showed which were primarily on perio and ortho rinses shouldn't be confined to just those perio and ortho rinses since the regular prevention rinse doesn't show the same results at all. In other words, I'm having a problem trying to figure out how you describe these different rinses to the public, given the fact that the concentration of ingredients changes and, therefore, what applies to one may not apply to the others.

DR. DRAKE: In my opinion, the way I see it, the regular prevention rinse is something, as I told Dr. Wu, something that would be used to kind of control the flora, so you wouldn't see the appearance of overgrowth perhaps of select organisms.

The clinical trial that we did with the regular prevention, you're right, we did not see a whole lot of changes in the microflora. So it may be that with diseased patients particularly, if there is going to be an application of the rinse, then you would have to go to the higher concentrations. Is that what you're looking for?

DR. LISTGARTEN: In other words, I'm thinking in terms of possibly labeling these products. I think clearly there are differences between the regular and the higher concentrations and, therefore, somehow one has to take that into account.

DR. DRAKE: I think so, absolutely.

CHAIRMAN GENCO: Just for clarification, this clinical trial that you showed was with the regular?

DR. DRAKE: That was with the regular.

CHAIRMAN GENCO: And then, of course, the

orthodontic.

DR. DRAKE: And the orthodontic. We have not, at Iowa, done anything with the perio except for that one laboratory study.

CHAIRMAN GENCO: Were there any statistically significant differences with either in any of the organisms? You mentioned strep mutans. Was that with the orthodontic that was reduced?

DR. DRAKE: That was with the orthodontic rinse.

CHAIRMAN GENCO: But it wasn't reduced with the regular.

DR. DRAKE: No. It came -- the statistics came out -- they were borderline. In other words, if you used the arbitrary cutoff to .05, we had a lot of those groups that hovered around .08, .09, 0.1, to you can argue if it's one of those things that's not statistically significant, but it's close.

CHAIRMAN GENCO: It's a trend. Okay.

DR. DRAKE: It's a trend.

CHAIRMAN GENCO: Fred.

DR. HYMAN: I saw that you had mentioned that

plaque indexes and gingival indexes were taken at various time points. I realize that your talk focused here on the microbiologic aspects, but as a way of tying that in, will those data, or have those data, been presented about the outcomes of gingival and plaque indexes?

DR. DRAKE: I personally have not presented them. I don't know if Dr. Douglas has presented. We had all that in a final report to Prevention Laboratories in 1993, but I don't know --

DR. LISTGARTEN: Max, maybe you can clarify that.

DR. LISTGARTEN: Actually, the data can be found in the OTC Volume 210,390. There are clinical data for both the control group, the regular group, and the ortho group.

CHAIRMAN GENCO: Further comments from the panel? Yes?

MS. ALTAIE: Sousans Altaie, clinical microbiologist, Division of Anti-Infective Drug Products, FDA. I have a question about the way you sample these patients when you are sampling the plaques,

and what teeth did you sample, and if it was a repeated sample of the same teeth?

DR. DRAKE: The teeth that were used I described as the four first molar teeth, and they were sampled using sterile curettes, and those plaque samples were pooled, and pooled into pre-reduced transport media and then processed in the laboratory. And then those same teeth then were sampled throughout the study.

MS. ALTAIE: Every time you say that the same teeth is sampled in a biofilm condition, I get worried about disturbing the ecology of a biofilm, and that when you sample the next time you are not dealing with the same thing again. Is there any way that these studies can go around this biofilm disturbance by designating different sets of teeth that gives us the same study out of the same mouth, and not bias the biofilm formation?

DR. DRAKE: That's a controversial issue. You are touching on the basics of the "Eisenberg principle of uncertainty" that just by measuring something, you are changing that, and that's really difficult to get around. That's why we did have a control group so we're measuring the same teeth in the control group as we did

in the active rinse group. But you're right, just the act of going in and measuring, taking a subgingival plaque sample, for example, and if you're going to take one down the line, you've already disturbed that microbial ecology, but that's the way you have to do it.

CHAIRMAN GENCO: Dr. Listgarten, do you want to comment on that?

DR. LISTGARTEN: We've actually done studies on that once upon a time, and it takes about six weeks for the biofilm to get back to its original composition. We didn't look at all the organisms, but using morphoea-type differential counts, by six weeks you get back to baseline.

CHAIRMAN GENCO: That's for supragingival plaque?

DR. LISTGARTEN: Subgingival plaque.

DR. DRAKE: Perhaps that might be more rapid with supragingival plaque, but I don't know.

CHAIRMAN GENCO: Okay. Further comments? Gene?

DR. SAVITT: If the stronger concentration mouthrinse seems to have some effect and the regular

concentration mouthrinse seems to have little or no effect, why is there a product that -- why are they marketing a mouthrinse that has little or no effect, and perhaps -- I don't know if you are the right person to answer that -- but is there a difference in taste between the lower concentration and the higher concentrations?

DR. DRAKE: I tnink Dr. Douglas probably should address -- I don't really have an opinion one way or the other on that, but I understand your question.

DR. DOUGLAS: The orthodontic strength has five times the active as the everyday. The periodontal has ten times the active as the everyday. The three concentrations was developed because of the clinician being able to select the strength that best fits his patient's needs. There's some people -- and we have slides like Dr. Mark Bernstein who did the tissue toxicity study at the University of Lowell. He had three patients that had one or two minor areas of inflammation, could never be cleared up. The everyday strength is targeted toward people like that that might have one or two minor areas, need a little bit of help,

and you're not using a harsh chemical that might potentially imbalance the oral flora. We increased the concentrations of the actives with the kids with the bracus because the everyday strength wasn't giving the clinical results that we wanted to see. After we did that, then we kept increasing 'til we got to the periodontal strength. And the ADA testing that's going on right now is with the periodontal strength.

DR. DRAKE: If I could add a real quick comment on your question about the prevention rinse, when we look at the total cell counts, you're right, we didn't really see any statistically significant differences. But from the laboratory studies, it's intriguing to me that even diluting the normal strength rinse out eight-fold, that you see an effect on growth of a single organism, you have a bacteriostatic effect and also a short-term inhibition of assopression. So it's conceivable that use of such a rinse over time, since the zinc in there would accumulate within the plaque matrix, that might have an effect. I don't have data to support that, but that's just a professional --

CHAIRMAN GENCO: Dr. Listgarten.

DR. LISTGARTEN: I think one of the problems we have to keep in mind is that in vitro testing, particularly if you test in planktonic suspensions, has no bearing on the effect in the mouth where you're actually dealing with a biofilm. So you may need ten times, hundred times the concentration to have an effect on biofilms. So, I think from a general standpoint, the test in planktonic suspension is useful to demonstrate that, indeed, there is an antimicrobial effect, but the proof is going to be in the clinical trials.

DR. DRAKE: And we do do a lot of laboratory based biofilm research because I agree completely with that, obviously, but we just haven't done it with this particular rinse. But you're right, sometimes you see marked effects using planktonic cells, then you actually go to a biofilm model and it takes a lot more of whatever the active compound is as the in vitro effect, but we do that.

CHAIRMAN GENCO: Okay. Any further comments or questions? Chris?

DR. WU: David, is this an alcohol-base rinse, or a water-base?

DR. DRAKE: It's low alcohol/no alcohol. Dr. Douglas?

DR. DOUGLAS: It's 1.6 alcohol for the everyday rinse, and 2.6 in the periodontal rinse.

DR. DRAKE: Okay. Low alcohol.

CHAIRMAN GENCO: Further comments or questions?

(No response.)

If not, I'd like to thank you, Dr. Drake.

We will now proceed to Dr. Sam Amer, of Sam Amer and Company, Incorporated, who will discuss the safety and efficacy of unsaponifiable fraction of corn oil.

DR. AMER: Good morning. Let me first introduce myself. I am a pharmacologist and not a dentist.

The unsaponifiable fraction of corn oil is in fact an extract of a natural food, corn oil. The process of preparing this material is very simple. You take corn oil and saponify it in the usual process of producing soap -- in other words, adding alkali to it -- and then extracting the mixture which contains the soap

and other ingredients with an organic solvent. What you get is the nonfat component of corn oil.

Chemically, it is composed of a mixture of plant sterols, major among which are tocopherols, vitamin E, sitosterol, stigmasterol among sever other minor components. To standardize the preparation, we have an elaborate system of tests to keep the concentration of the major components within very well defined ranges. The product is not a new one. It is an old one that has been on the market for over 30 years in France and several other countries, so it is not a new thing. The only thing is we wanted to make sure that the preparation which has been in use for such a long time abroad, is exposed to some critical clinical studies here to support efficacy claims in this country.

So, the safety of the unsaponifiable fraction of corn oil has been well demonstrated both in animals and man. In animals, a full complement of toxicology has been done, including acute, subacute and chronic toxicology in several species. And basically one could say that it is very difficult to produce toxic effects with this material.

As far as the safety in people, at least ten million people have been exposed to this material either in tablets or in drops, which they use in France, or as a toothpaste. The only side effect that has been shown to exist with this material is that some people are sensitive to corn and corn products and they develop some allergies, and these are completely removed once the product use is stopped. So, other than this allergic reaction, no toxicity has ever been described for this product. In animals, it has no teratogenic activity or any other toxic effect even at extremely high doses.

The effects of the unsaponifiable fraction of corn oil on tooth plaque and gingivitis was discovered by accident. The product has been known for many years to be good for scleroderma as a cream, and the clinician developing the product for this use discovered, and the patients realized, that the teeth mobility and the mouth odor has been vastly improved.

So, we decided to do a number of studies to establish its value in plaque and gingivitis. Up to now, there are 24 clinical studies, two of which were

done in the United States, eight of which are double-blind placebo-controlled. All show that this product is effective in treating gingivitis and plaque.

The latest study was done at the University of Pennsylvania by Professors Yankell and Emling, and in this study it was shown that a 1 percent toothpaste containing the unsaponifiable fraction of corn oil produced statistically significant reductions in both the plaque and gingivitis score, using 42 subjects. No effects on either soft or hard tissue in the mouth were observed.

From a mechanistic point of view, really, the exact mechanism by which this material produces these effects is really unknown, although in animal studies it has been shown that unsaponifiable fraction of corn oil has an effect on bone resorption and an antiinflammatory effect as well.

From a theoretical standpoint, this may not be very surprising since the structure of its major sterols is quite similar to the steroids and to vitamin D structurally. So, maybe we're having some mild vitamin D or steroid side effect, but the exact mechanisms

really have not been established.

It seems to me that since the product has been shown to be effective in many double-blind placebo-controlled studies and its safety is unquestioned, that it should be made available to the American public. Thank you.

CHAIRMAN GENCO: Thank you, Dr. Amer. Any comments or questions from the panel? Chris?

DR. WU: I have a question. You talked about the 24 clinical studies that you have done, and you say that your product is effective against gingivitis and so forth. Are you talking about a product that -- you are talking about a corn oil that is in the Insadol (phonetic) product and not the product we're supposed to review.

DR. AMER: Yes.

DR. WU: That's a product that people would take systemically. They would take a teaspoon of oil every day for the prevention of gingivitis and so forth.

DR. AMER: No, no. Let me clarify this one. The product that's marketed in France under the name Insadol is in the form of tablets. Each tablet contains

35 mg of this unsaponifiable fraction of corn oil. There is no oil in teaspoons. And the same product also is available in drops. You take the drops and put them in a glass of juice and drink the juice. The drops contain also the unsaponifiable fraction of corn oil. The toothpaste which is marketed under the name of Perodine (phonetic) is also containing the unsaponifiable fraction of corn oil. So we are all talking about the same unsaponifiable fraction of corn oil that was used in all these studies.

CHAIRMAN GENCO: Do you want to pursue that?

DR. WU: That's okay.

CHAIRMAN GENCO: The study you quoted, the Yankell study, was with the toothpaste?

DR. AMER: Yes.

CHAIRMAN GENCO: And you are presenting studies with the systemically ingested also?

DR. AMER: Yes. These were not studies done by me, these were studies in the literature.

CHAIRMAN GENCO: Okay. Thank you. Further comments? Questions?

(No response.)

Okay. Thank you very much, Dr. Amer.

We will proceed now to reviews of the U.S. marketed ingredients. The first is a summary of a review that was presented before by Dr. Listgarten, on the zinc chloride/sodium citrate/hydrogen peroxide/SLS prevention mouthrinse preparation.

DR. LISTGARTEN: I should preface my comments by saying that when this report was written, I may not have had access to all the documentation that I saw on my desk this morning, including a booklet on the prevention mouthrinse, and maybe some of the data that was presented as well. So this report is basically a reflection of the data that was available at the time that I received the documentation.

I should also point out that when I reviewed the documentation and compared the ortho and perio formulations to the regular mouthwash, it was my impression that the concentration of ingredients varied up to about three to five times the concentrations in the regular prevention, but this morning I heard it mentioned that perio and ortho formulations in fact had five to ten times the concentration of the ingredients.

So I'm a little bit confused because the documentation that was available to me seemed to indicate up to five times the concentration, and I heard it mentioned this morning that it was up to ten times in some of the products. So I will stick with my original report for the time being. If there is a need to change this, I suppose it can be changed.

Prevention mouthrinse is a combination of several active ingredients that are used together. The mouthrinse is produced in three formulations described as "regular strength", "ortho strength", and "perio strength". All of the active ingredients have potentially useful properties when included in a mouthrinse. It is not clear, however, how this complex mixture behaves under conditions of normal use.

The active ingredients are sodium lauryl sulfate, zinc chloride, sodium citrate, and hydrogen peroxide. Hydrogen peroxide is directly incorporated into the regular formulation which is dispensed as a single bottled product. In the other two formulations, the rinses are dispensed as twin bottles, one of which contains the hydrogen peroxide. The consumers mix the

contents of the two bottles just prior to rinsing.

The ortho and perio formulations have 2.5 to five (sic) times the concentration of the active ingredients found in the regular formulation, including 1.5 percent hydrogen peroxide versus the 0.6 percent for the regular formulation. The perio rinse also has five times as much zinc chloride as the regular rinse.

The proportions of the ingredients vary among the three formulations, but are generally found in relatively low concentrations. The concentration ranges for the active ingredients are as follows -- and that's from OTC Volume 210,001: sodium lauryl sulfate, the range varies from 0.06-0.15 percent; zinc chloride varies from 0.016-0.08 percent; sodium citrate varies from 0.024-0.12 percent; and hydrogen peroxide varies from 0.595-1.5 percent.

The individual ingredients appear to be safe at the concentrations used, at least according to the individual ingredient reviews presented elsewhere during these meetings. However, since the above ingredients are used in combination, their efficacy in achieving the stated aims of the product as well as the safety of the

product formulations must be examined under conditions of combined use. This is the purpose of this report.

Acute toxicity tests in rats indicate that the prevention mouthrinse formulations tested, although it's not clear always which formulation is being tested, is relatively non-toxic. The purpose of the study was to assess the toxicity of the product administered orally as a single dose to Sprague-Dawley rats, followed by a 14-day observation period.

The product was administered by oral gavage to five male and five female rats at a dose of 40 g/kg body weight. Over the following 14 days all animals survived in apparently good health, although they exhibited hunched postures and loose stools for the first two days. No abnormal findings were observed at macropsy. This dose is considerably higher than the likely intake by subjects using the product as a rinse.

The results of a proposed 30-day study of the effect of topical application of the product to hamster cheek pouches which was mentioned in OTC Volume 210,035, were not available to this reviewer.

Mechanisms of action: Zinc chloride is used

for its antibacterial properties and its ability to reduce plaque accumulation and acid production by plaque bacteria. In the presence of sodium lauryl sulfate, the antibacterial effect of zinc salts may be enhanced.

Sodium lauryl sulfate is used for its emulsifying and antiplaque formation properties. Hydrogen peroxide is used for its antibacterial and foaming properties. Sodium citrate is used as an astringent to enhance the antibacterial activity of zinc chloride.

The recommended uses for the combination product include post-surgical care, gingival hemorrhage, aphthous ulcer treatment, mucosal injury from removable dental appliances, pit and fissure cleansing, puberty gingivitis, as a pretreatment rinse two weeks prior to periodontal treatment, cleansing around orthodontic arch wires and brackets, safeguard against decalcification and reduction of plaque accumulation at the gingival margin. That's according to OTC Volume 210,001.

Results from in vitro studies: In one study, the effect of the combination product was tested on acid production by strep mutans, and we saw some of the data

this morning. The experiment consisted of three experimental groups: strep mutans in enriched growth medium, which served as a control; strep mutans in enriched growth medium exposed for various durations of time to a four times diluted prevention mouthrinse; and s. mutans in enriched growth medium exposed for various durations of time to eight times diluted prevention mouth rinse.

After a five-minute exposure, the cells were centrifuged, washed resuspended in product-free medium and incubated. The viability of the bacterial was not affected by the exposure to the product, as was also shown this morning. Therefore, the product at concentrations of four and eight times dilutions did not kill bacterial during a five-minute exposure. However, acid production by strep mutans was inhibited for eight hours as a result of this exposure, compared to the control.

The second study, in which the antimicrobial activity of the combination product was tested in vitro. This study was carried out by Dr. Drake, from the Dow's Institute at the University of Iowa. The documentation

in the material that was available to me did not include the details of the experimental protocols.

Essentially, the study consisted in exposing a spectrum of all microorganisms to various concentrations of the prevention mouthrinse in vitro. However, how this was done was not described in the volume that I consulted. The bar graphs indicate various degrees of inhibition of the bacteria tested at various dilutions of the test rinse. It should be noted that under the protocol of this particular study, streptococcus mutans was inhibited by dilutions of the mouthrinse as high as 1:32 -- in other words, there are 32 dilutions of the mouthrinse. However, in the previous study I referred to, the mouthrinse appeared to have no antibacterial effect even at dilutions of 1:4. So there seems to be a discrepancy in the data that I consulted between those two studies.

I had data available from one clinical trial organized as a blinded parallel treatment design of six weeks duration which was carried out to compare the relative efficacy of the three product formulations on plaque and gingivitis in a human adult population.

Group one used a commercial toothpaste and toothbrush; Group two used a regular product and a commercial toothpaste and toothbrush; Group three used the ortho product and a commercial toothpaste and toothbrush.

Following the baseline examination, each subject was instructed to brush twice a day and, if assigned to a mouthrinse, to use the rinse after brushing.

Baseline and six-week data included the gingival index of Loe and Silness recorded on six surfaces per tooth, the Plaque Index using Turesky's modification of the Quigley and Hein Index, and a mean score per subject was calculated for each index.

Essentially, what the data showed was a slight reduction in plaque index, but essentially no change in the gingival index.

Although the reduction in the gingival index score was statistically significant for all three groups, the clinical significance of this reduction was marginal at best. There was no statistically significant difference among the three groups.

The plaque index reduction was statistically

significantly better for the rinse group than the controlled group. However, it should be pointed out that the controlled group lacked a placebo rinse to determine whether the difference in plaque reduction was due to the rinsing effect to which the controlled subjects were not exposed, or to some of the active ingredients in the test rinse. The degree of plaque reduction for any of the groups, again, is of questionable clinical significance.

The documentation also included data collected in individual dental offices by dental practitioners. Again, there were no experimental protocols for these studies which appear to lack the basic requirements for controlled, randomized clinical trials. Therefore, the results presented are of questionable value.

Unless the outcome of the safety review of the individual ingredients indicates otherwise, and they don't seem to, it is likely that the product is safe for use as a mouthrinse. The rather meager animal and clinical data available fail to support the claims made for this product under the indications that I read out. Therefore, while the product may well be safe, it is not

considered to be effective for the indications listed or, if it is effective, that remains to be shown. Thank you.

CHAIRMAN GENCO: Thank you very much. Are there any questions of Dr. Listgarten? Bill?

DR. BOWEN: Max, do you have any information on the pH of the solutions? I'm concerned about two ingredients. One is obviously the EDTA that I mentioned, the other is sodium citrate, which also a chelator of calcium. And it is conceivable -- although, obviously, I have no data -- that this combination could in fact promote caries with chronic use if the pH is of the right value.

DR. LISTGARTEN: I don't have any information on that.

CHAIRMAN GENCO: Was any caries data presented in the clinical study?

DR. LISTGARTEN: Not that I can recall.

DR. DOUGLAS: The pH of the everyday strength stays between 3.9 and 4.5. The pH of the base site for the ortho and the perio stays between 5.9 and 6.1.

CHAIRMAN GENCO: Thank you. Further comments?

Questions?

(No response.)

Are we ready for a vote?

Okay. Let's take safety first. What is your recommendation? You were quite explicit about the fact that each of these agent's ingredients alone, with the possible exception of EDTA, alone might be safe, but the combination was tested in one acute rat experiment and 30-day hamster pouch experiment wasn't reported.

DR. LISTGARTEN: The animal testing was primarily to see if there were some medical effects from using very, very high doses and, as I indicated, the animals survived very, very high doses. So, from that standpoint, the ingredients are probably safe, or the product, even in combination, is probably safe. The issue of demineralizing teeth over the long-run is one that obviously Dr. Bowen is concerned about, but about which we have no data.

It's interesting that the conventional product seems to have a much lower pH than the products with the higher concentrations. Whether this is significant when it is used as a mouthrinse for a brief period of time,

I'm not sure. I suspect the pH returns to normal rather quickly.

At this point, I would say that the product is safe as far as a mouthrinse is concerned.

CHAIRMAN GENCO: As a combination.

DR. LISTGARTEN: As a combination.

CHAIRMAN GENCO: So you would suggest Category I then?

DR. LISTGARTEN: I would suggest a Category I from the standpoint of safety. I don't believe that the low pH would persist for very long following regular use of the product.

DR. SAVITT: Max, I have a brief question for you. Is this for safety for the regular product, and do you have any safety concerns about the products that have much higher concentrations?

DR. LISTGARTEN: Even at higher concentrations, the ones that are used are comparatively low compared to what is considered toxic. So I think there is a big margin of safety here even with the products that have the higher concentrations.

CHAIRMAN GENCO: Further comments on the

safety of the mixture?

(No response.)

Are we ready for a vote then. The recommendation is for Category I. Let's take that as a motion then.

DR. LISTGARTEN: I'd like to move that for safety purposes this be classified as a Category I product.

CHAIRMAN GENCO: Second to that?

DR. SAVITT: Second.

CHAIRMAN GENCO: Seconded by Dr. Savitt. Okay. Let's go around the table. Voting members. Dr. Bowen, what's your vote?

DR. BOWEN: No, for the reasons I've already indicated.

CHAIRMAN GENCO: Dr. Listgarten?

DR. LISTGARTEN: Yes.

CHAIRMAN GENCO: Dr. Savitt?

DR. SAVITT: Yes.

CHAIRMAN GENCO: Dr. Saxe?

DR. SAXE: Yes.

CHAIRMAN GENCO: Dr. McGuire-Riggs?

DR. McGUIRE-RIGGS: Yes.

CHAIRMAN GENCO: Dr. Wu?

DR. WU: Yes.

CHAIRMAN GENCO: Dr. D'Agostino?

DR. D'AGOSTINO: Yes.

CHAIRMAN GENCO: Dr. Altman?

DR. ALTMAN: Yes.

CHAIRMAN GENCO: Okay, fine. So the vote is seven yes and one no, so it's Category I recommendation.

Okay. Let's proceed now to efficacy. I'm sorry, Lew.

MR. CANCRO: Dr. Genco, just a point of clarification. Perhaps the FDA Administrator can answer this. Is the consumer representative a voting member of the panel?

DR. SHERMAN: I think under NDAC the consumer rep is a voting member. I know in the past they haven't voted. It wasn't until recently that the subcommittee was actually a part of NDAC, so in the past the consumer rep has not voted.

CHAIRMAN GENCO: Is that clear?

MR. CANCRO: Yes.

CHAIRMAN GENCO: Okay. Let's proceed now to efficacy. What I heard was a six-month study with some plaque inhibition, but not gingivitis.

DR. LISTGARTEN: At the time when I had access to the data, I did not have six-month data available. The six-month data was presented to us this morning, and it was only in terms of microbiological data. So the only data that was available at the time I reviewed the product was -- let me make sure I am not misquoting it -- was six-week data.

CHAIRMAN GENCO: Were we presented with the six-month data today?

DR. LISTGARTEN: Not the clinical.

CHAIRMAN GENCO: Not the clinical results.

DR. LISTGARTEN: No.

CHAIRMAN GENCO: But do we have it in written form?

DR. LISTGARTEN: No, unless it's in that booklet that I just picked up but hadn't had a chance to study.

CHAIRMAN GENCO: Is it in that booklet?

DR. DOUGLAS: Yes. It was submitted, and we

made four different submissions, and the tissue toxicity study was also submitted --

DR. LISTGARTEN: I seem to find six-week data, I didn't seem to have six-month data.

CHAIRMAN GENCO: Would you please go to the microphone, we have to get this -- Dr. Douglas, identify yourself again for the record.

DR. DOUGLAS: Dr. Douglas. Yes, we did make submission of the six-month clinical that was done at Iowa, and we also made submission of the tissue toxicity studies, and I can go back and dig out the date and the submission numbers, the volume numbers. I don't have them with me right now.

DR. LISTGARTEN: Actually, as I look through the booklet, all you have in the booklet is six-week data, there is no six-month data in the booklet either.

DR. DOUGLAS: The University of Iowa trial?

DR. LISTGARTEN: The data shown on page 42 is six-week data.

DR. DOUGLAS: May I get one of the books, please?

CHAIRMAN GENCO: Perhaps what we're going to

have to do is maybe to clarify what was submitted, and then defer the vote because it sounds like there's more data that might be relevant.

DR. DOUGLAS: There were four different submissions to the FDA, and I apologize for not having that with me, but I can get that to you.

CHAIRMAN GENCO: We should get this sorted out before we take a vote. It may not be able to be done at this meeting -- we will try to do it at this meeting -- so if you are available, you can help us sort that out. Otherwise, we can defer it to another meeting. I think, in fairness, we really have to have the full analysis of all the data submitted. Anybody feel otherwise on the panel?

(No response.)

Okay. Thank you. So we've tabled that vote until we get the clarification of the full data.

I think the safety issue also, even though it is Category I, that has to be looked at again, too, if there is more safety data.

So, let's proceed then with the stannous pyrophosphate/zinc citrate, and this is a new

presentation by Dr. Saxe.

DR. SAXE: You have a draft of my report. The draft that you see was prepared and I wasn't in the shop, I've been away for a while, and apparently the spellcheck that I asked be used wasn't done, so I apologize for those things. Let me give my report.

Stannous pyrophosphate and zinc citrate: This data was reviewed, the data that was submitted by the company was reviewed looking at if there was sufficient data to justify whether the product, the combination product, was safe as an antigingivitis product, and also effective as an antigingivitis product.

Stannous pyrophosphate has the chemical formula $Sn_2P_2O_7$ and has been described as a free-flowing, odorless white to off-white powder. The commercial foam of stannous pyrophosphate in anhydrous stannous pyrophosphate. This agent has been chosen for use in a dentifrice based on prior demonstrated antibacterial effects which effects have been ascribed to the soluble stannous ion.

Zinc citrate has the chemical formula $Zn_3(C_6H_5O_7)_2$ and is prepared from zinc carbonate and

citric acid. The commercial form of zinc citrate is zinc citrate trihydrate, $Zn(C_6H_5O_7)_2 \cdot 3H_2O$, and has been described as a white, odorless powder, smooth to the touch and free from grittiness, slightly soluble in water. This agent has been chosen for inclusion by the submitters in a dentifrice in combination with stannous pyrophosphate because of reported antiplaque as well as anticalculus efficacy.

Safety. Each of the two agents used in the combination, zinc citrate and stannous pyrophosphate, based on animal studies plus human use, does not appear to present a risk in terms of acute toxicity, chronic toxicity, reproduction toxicity, genotoxicity, carcinogenicity, phototoxic sensitization, or oral irritation.

Oral ecology studies to ensure that the long-term use of antimicrobial agents does not result in a significant change in the balance of the normal oral flora, were done. In a 21-day experimental gingivitis study, Jones and Ritchie, 1990, and a six-month clinical trial, Jones, et. al., 1991, following use of a dentifrice containing stannous pyrophosphate, 1.0

percent, and zinc citrate, 0.5 percent, no significant changes in plaque flora, no increase in opportunistic organisms in saliva and no development of resistance were seen, again, as reported by the submitters of the data.

Effectiveness. Data submitted to provide evidence of clinical efficacy of a fluoride toothpaste containing stannous pyrophosphate at 1.0 percent and zinc citrate at 0.5 percent as an antiplaque and antigingivitis product is based on four studies: an 18-hour plaque growth inhibition test; a 21-day experimental gingivitis trial; a 12-week motivational brushing trial, and a six-month normal use clinical trial.

The plaque growth inhibition studies used an 18-hour protocol described by Harrap in 1974, to test the combination dentifrice for its effect on plaque growth in vivo. It was reported, Lloyd, 1991, the formulation reduced plaque significantly compared to a placebo toothpaste and thus showed the antimicrobial activity of the two agents seen n vitro is retained when formulated into a dentifrice and delivered into the oral

cavity.

The 21-day experimental gingivitis study, Saxton and Cummins, 1991, enrolled 37 subjects who were brought to a state of no gingival inflammation following four weeks of repeated professional cleaning and oral hygiene instruction. One posterior lower segment of teeth was covered with a vacuum-formed tooth shield, as described by Bosman and Powell in 1977, and subjects instructed not to brush that segment which was covered when the subjects cleaned the remainder of their dentition. The tooth shields also served as carriers for the daily application of control and test toothpastes. Assessment of inflammation and bleeding was done at baseline and at three weeks. Mean scores were significantly lower for the test group at three weeks, interpreted by the submitters of the data as the test combination dentifrice better delaying the development of gingivitis.

The 12-week motivational brushing trial, Gaare, et. al., 1991, included 81 adult subjects described as receiving a prophylaxis and motivation at baseline and then used the combination dentifrice at

least twice daily. Plaque index and gingival index scores improved at six weeks, plaque scores continue to improve at 12 weeks, and bleeding scores were maintained at 12 weeks.

The six-month normal use clinical trial, Saxton, et. al., 1991, enrolled 268 subjects of whom 251 completed the six months. Clinical assessments were made at baseline and at 1, 4 and six months. Tooth scaling and polishing was done after baseline assessments included plaque index of Loe, modified gingival index of Lobene, extrinsic stain indices, Lobene, Davis and Re, supragingival calculus, Valpe, and gingival bleeding, Ainamo and Bay. The results at six months showed no difference in mean plaque scores and no difference in mean modified gingival index scores. Gingival bleeding was statistically significantly lower for the test group, $P<0.01$, as was the mean calculus scores, $P<0.01$. Toothstaining area mean scores were reported and the test group was statistically significantly higher at a $P<0.05$, and stain intensity mean score was also higher for the test group at $P<0.001$. It was reported that 17 percent of the test

group observed toothstaining for themselves. Tongue staining was clinically detectable in approximately 40 percent of test dentifrice subjects compared to approximately 10 percent of control dentifrice subjects, 53 versus 15 subjects at six months.

Evaluation. In my opinion, the combination of stannous pyrophosphate at 1.0 percent and zinc citrate at 0.5 percent in a dentifrice does not present a risk based on evidence submitted, and maybe considered safe.

In my opinion, there is insufficient evidence of the efficacy of the combination dentifrice as an antiplaque/antigingivitis product, as promoted by the submitters of the data. Further clinical trials are needed if such efficacy is to be shown.

CHAIRMAN GENCO: Thank you, Dr. Saxe. Are there any comments or questions? Gene?

DR. SAVITT: Stan, I notice that in the 12-week brushing trial, the gingival index score improved at six weeks, but there's no mention at 12 weeks. Should I take it that there was no effect at 12 weeks?

DR. SAXE: No further improvement.

CHAIRMAN GENCO: Chris?

DR. WU: I just want to clarify one point. You read on page 2, the first paragraph, the third line -- it was testing effect on plaque growth in vitro, but you read in vivo. So is it --

DR. SAXE: Did I read in vivo?

DR. WU: Yes.

DR. SAXE: I was reading my handwritten draft instead of that. In vivo was correct.

CHAIRMAN GENCO: Are you clear, Chris?

DR. WU: So we should change the draft from in vitro to in vivo, right?

DR. SAXE: Yes. There were other typographical errors as well.

CHAIRMAN GENCO: Lew?

MR. CANCRO: Stanley, two questions concerning the point that Gene raised. The first is, the six-week improvement observed in the 12-week motivational brushing, I presume, was significant? You don't say that, but my assumption is that it was.

And the second question is, did it maintain that benefit at 12 weeks, meaning was it still significant at 12 weeks? You say it didn't continue to

improve, but was the magnitude of the benefit maintained at 12 weeks?

DR. SAXE: Okay. As me -- this is July '91 -- there were 23 volumes, and I have the last two studies I think I pulled out. I didn't pull out that one. Ask me the questions again, please, Lew, and I will attempt to give you an answer.

MR. CANCRO: Concerning the 12-week motivational brushing study, you make the statement that gingival index scores improved at six weeks.

DR. SAXE: Correct.

MR. CANCRO: And the question I'm asking you, was that statistically significant?

DR. SAXE: The six weeks?

MR. CANCRO: Yes, at six weeks.

DR. SAXE: Yes, there was an improvement at six weeks, but it then dropped off. Plaque was significantly improved at 12 weeks. I can't say for sure. My feeling is now -- it's been a while -- that there was a six-week improvement, and that was it for the gingival index scores.

MR. CANCRO: So they reverted, or they

maintained, or --

DR. SAXE: I'm not sure of that. There was an improvement in both plaque and bleeding scores at 12 weeks, but not the gingival index score. And I'm sorry, I don't have the original studies here.

CHAIRMAN GENCO: Stanley, in the six-month clinical trial, there's no reduction in plaque, no reduction in gingival index, but there was a reduction in the bleeding index. Is there any reason to believe that this combination would have an antigingivitis effect aside from an antiplaque effect? In other words, in the absence of an antiplaque effect, does it have antiinflammatory activity or mechanism?

DR. SAXE: That's the possibility that exists, but, again, this was one isolated report. I mean, this is a number of clinical trials of no less than one, and that's why I say there is insufficient data. I'm not saying that that was -- I'm accepting that, that at six months there was decreased bleeding, but I can't base on that one finding in that one study that that -- I cannot say there was sufficient -- I would say there is insufficient evidence then at this point to --

CHAIRMAN GENCO: So there's no strong evidence that this would be an antiinflammatory or have an effect other than antiplaque to reduce gingivitis if, indeed, it did?

DR. SAXE: There's no evidence that the antiplaque -- that it's effective either in the longer-term. Again, one study but six months, and that showed no evidence of antiplaque activity.

CHAIRMAN GENCO: Okay. So this material was presented in '91, to the FDA?

DR. SAXE: Correct.

CHAIRMAN GENCO: Are we aware of anything else being presented since then?

DR. SAXE: I was not given any further documentation with this combination.

CHAIRMAN GENCO: So based upon what we're seeing here, there could be a vote, but it may be premature.

DR. SAXE: Yes. I would suspect there was not a lot of enthusiasm to pursue this given the toothstaining and the intensity of toothstaining that showed up at six months.

CHAIRMAN GENCO: We have a choice. We could defer this maybe to the next meeting and wait and see if there's more submission, or we could take a vote today.

DR. SAXE: I would say that if there were detailed reports and we were uncertain, my own feeling is that I'm proposing that in terms of the safety of the product, that it would be Category I. That in terms of the efficacy, it is Category III, insufficient data yet.

CHAIRMAN GENCO: Okay. So that's certainly a possibility.

DR. SHERMAN: It would be fine to vote today. If there is a response next meeting, we can consider that also.

CHAIRMAN GENCO: Okay, good. Max?

DR. LISTGARTEN: I was just going to say if there is, in fact, another clinical trial that has been completed, the results of which we don't have, I can see postponing it. But if, in fact, there are no additional data forthcoming, I don't see any reason for postponement.

CHAIRMAN GENCO: Okay. As Bob said, the individuals could submit between this and the next

meeting, if there was more data, we can consider it. Okay. Stanley, do you want to make a motion with respect to safety then?

DR. SAXE: Yes. With respect to safety of this combination product of stannous pyrophosphate and zinc citrate, I would make the motion that it be Category I for safety.

CHAIRMAN GENCO: Is there a second to that?

DR. LISTGARTEN: Second.

CHAIRMAN GENCO: Dr. Listgarten seconds that. Any discussion? Further discussion?

(No response.)

If not, let's proceed to the vote. Let's start with Dr. Altman.

DR. ALTMAN: Yes.

CHAIRMAN GENCO: Dr. D'Agostino.

DR. D'AGOSTINO: Yes.

CHAIRMAN GENCO: Dr. Wu.

DR. WU: Yes.

CHAIRMAN GENCO: Dr. McGuire-Riggs?

DR. McGUIRE-RIGGS: Yes.

CHAIRMAN GENCO: Dr. Saxe.

DR. SAXE: Yes.

CHAIRMAN GENCO: Dr. Savitt.

DR. SAVITT: Yes.

CHAIRMAN GENCO: Dr. Listgarten?

DR. LISTGARTEN: Yes.

CHAIRMAN GENCO: Dr. Bowen.

DR. BOWEN: Yes.

CHAIRMAN GENCO: Okay, thank you.

Let's proceed now to the efficacy. Stan, do you want to make a motion?

DR. SAXE: Yes. I would make a motion that the combination product of stannous pyrophosphate at 1.0 percent and zinc citrate at 0.5 percent be in Category III, insufficient data.

CHAIRMAN GENCO: Is there a second to that motion?

DR. D'AGOSTINO: Second.

CHAIRMAN GENCO: Dr. D'Agostino seconds that.

Any discussion of that? Sheila?

DR. McGUIRE-RIGGS: No.

CHAIRMAN GENCO: You looked like you were getting prepared to say something.

DR. McGUIRE-RIGGS: To vote.

(Laughter.)

CHAIRMAN GENCO: If there's no discussion, let's proceed to the vote. Dr. Bowen.

DR. BOWEN: Yes.

CHAIRMAN GENCO: Dr. Listgarten.

DR. LISTGARTEN: Yes.

CHAIRMAN GENCO: Dr. Savitt.

DR. SAVITT: Yes.

CHAIRMAN GENCO: Dr. Saxe.

DR. SAXE: Yes.

CHAIRMAN GENCO: Dr. McGuire-Riggs.

DR. McGUIRE-RIGGS: Yes.

CHAIRMAN GENCO: Dr. Wu.

DR. WU: Yes.

CHAIRMAN GENCO: Dr. D'Agostino.

DR. D'AGOSTINO: Yes.

CHAIRMAN GENCO: Dr. Altman.

DR. ALTMAN: Yes.

CHAIRMAN GENCO: Thank you.

DR. D'AGOSTINO: Can I make a suggestion in terms of the report? What is going to happen with this

report? Is this going to be put into a particular document? What I'm getting at, I think it would be helpful if we have to go back to this, if we grace the report with open-label study, double-blind study, so forth. As we were going through it, I think your presentation made it clear what the studies were, but I think if we label it right at the top, then it makes it very forceful that we don't have a lot of clinical trial type data to back this --

CHAIRMAN GENCO: You're suggesting that in Dr. Saxe's report that the 21-day, and the 12-week, and the six-month are labeled as to what they are?

DR. D'AGOSTINO: As to what they are exactly.

CHAIRMAN GENCO: Are you suggesting that we also incorporate some suggestions as to what studies are needed, also?

DR. D'AGOSTINO: I wasn't going to make that suggestion, but that is a good suggestion, and I think we're talking about two clinical trials, you know, double-blind clinical trials. I thought that was inferred, but so that there's no confusion, I think that would be a useful statement.

CHAIRMAN GENCO: Okay. Stanley, would you do that in your revision, and then we'll get another chance to look at it at the next meeting.

Okay. We're finished with the U.S. marketed ingredients as far as we can go today. So, let's take a break and it's ten after 10:00. Can we get back at 10:30, and we'll start then the foreign marketed ingredients.

DR. SHERMAN: Bob, can I just make an announcement?

CHAIRMAN GENCO: One minute before you go. Bob Sherman has an announcement.

DR. SHERMAN: One of the ingredients that was reviewed by Dr. Riggs previously, Zylatol, has been withdrawn from the review. Two sponsors have sent written requests to FDA that they no longer wish to pursue it, so the subcommittee won't vote on that ingredient.

CHAIRMAN GENCO: Thank you. Okay. See you back here at 10:30.

(Whereupon, a short recess was taken.)

CHAIRMAN GENCO: Rhonda Stover has an

announcement to make.

MS. STOVER: I just wanted to clarify the voting status for this meeting. The industry representative does not vote, and the consumer rep for this meeting, since Dr. Altman is a member of the CDRH's Dental Products Panel, will not have a vote for this meeting. He is free for discussion, but there will be no vote. Thank you.

CHAIRMAN GENCO: Thank you. So let's start with the foreign marketed ingredient, Hexetidine, and Dr. Bowen is going to review this. I'd like, before we get started, to announce that this is for information only. We will not be taking a vote on any of these agents. The reason that we're reviewing them is to provide the FDA with this information in the event that later there is a question as to whether or not they should be included in the monograph or considered otherwise. So, this is for information purposes only. Dr. Bowen.

DR. BOWEN: Thanks, Bob.

In reviewing Hexetidine, I reviewed the information that was submitted and, in addition, I

carried out a literature search in case other material has been published since the original submission.

Hexetidine is also known as Glypesin, Hexoral, Hextril, Oraldene, Sterisil, Sterilate, Sterisol, and Triocil, to mention just a few. Chemically it is 5-amino-1,3-bis (2-ethylhexyl)-hexahydro-5-methylpyrimidine. Hexetidine is essentially derived from the compound pyrimidine. It has a molecular weight of 339, and it is poorly soluble in water but readily soluble in a range of organic solvents. Hexetidine was first synthesized in the 1940s. Its possible use as an antibacterial and antifungal agent is described in Appendix B of the submission.

Toxicity. In the submission, extensive toxicity studies have been described, and a literature search revealed several additional studies which may perhaps require some additional attention.

A mutagenicity study was carried out using Salmonella typhimurium as an indicator organism. Hexetidine was extremely toxic to the test strains, so a dose of 5 ug per plate was chosen as the highest level in mutagenicity tests. No mutagenicity was detected at

the dose levels used. A subacute oral toxicity investigation was also carried out in rats. Rats were fed a diet containing 1, 100, 300, or 1000 ppm for 13 weeks. No deaths were reported during the 13 weeks. However, animals offered diet containing 1000 ppm consumed less food and water than control groups and also gained less weight. These observations could be attributed to adverse taste of food containing Hexetidine.

Changes in blood chemistry were observed that are consistent with reduced food and water intake (hemoconcentration). There was also some evidence of impairment of liver function in animals exposed to 1000 ppm. Platelet counts were numerically higher in all groups exposed to Hexetidine and the increases observed appear related to the dose of Hexetidine. Several additional differences in blood chemistry values were also detected among the groups, e.g., lower glucose in females, all groups, elevated creatinine, 1000 ppm group, elevated cholesterol, 1000 ppm group, and elevated sodium, all groups. Differences in ratios of size of organs to brain were also detected among groups.

Teratology studies were also carried out in rats. Hexetidine was prepared in corn oil and was administered by gavage at doses of 50, 25, and 12.5 mg per kg body weight on days 6-15 of gestation. Control rats received corn oil. Some maternal toxicity was observed in the dams receiving the 50 mg/kg dose; there was reduced weight gain and reduced food and water intake. "Foetal abnormalities were not observed", nevertheless examination of the skeletons of 21-day-old pups revealed a significant increase in the total number of pups with defects, anomalies and variants in both the 50 and 2.5 mg Hexetidine/kg groups. These were attributed to an increase in the total number of pups in these groups with duplication of the posterior palatine foramen; they were not observed in the fetuses and "were not considered to be biologically relevant".

A series of acute studies was carried out using 99 percent pure Hexetidine. It was found that the LD_{50} in rats is 0.61 g/kg. Hexetidine was found to be a moderate irritant in the Draize primary irritation index, and to be corrosive in primary eye irritations. It was found to be non-mutagenic in the chromosome

aberration test.

It has been reported that Hexetidine may undergo nitrosation under acidic conditions with the formation of nitrosamines. That was conducted by Bae in 1994. The major nitrosamine produced termed "Hexno" forms rapidly in yields as high as 60 percent over the pH range 1-4.8 at incubation times of one hour at 37 degrees centigrade. The authors conclude that "the available data suggest the probable formation of Hexno and other nitrosamines from Hexetidine under conditions of its use". In the submission it is noted that "Although Hexetidine product stability is very good, specific storage conditions are required. The product shall be stored in the tightly closed original container, protected from light at temperatures not exceeding 6 degrees Centigrade. NB store carefully!"

The effect of Hexetidine on growth of buccal epithelial cells was explored using cell cultures. It was observed that exposure of cell cultures to even high dilutions of Hexetidine inhibited incorporation of thymidine, and formation of lactate dehydrogenase.

Antimicrobial effects. Hexetidine is an

effective antimicrobial agent against a wide range of gram positive and gram negative microorganisms. However, several organisms appear to be particularly resistant to its effects, e.g., Pseudomonas aeruginosa and Serratia marcescens. There are reports of persons acquiring nosocomial infections from solutions of Hexetidine contaminated by these organisms.

Several oral microorganisms, e.g., S. mutans, S. sanguis, Candida, are sensitive to Hexetidine but apparently less so than to other oral antiseptics. Sublethal levels of Hexetidine reduced the ability of mutans to adhere to surfaces. No systematic study of the effects of Hexetidine on other potential oral pathogens appears to have been carried out. The salivary flora appears to recover to pre-rinse levels in 90 minutes.

Clinical studies. The number of clinical studies conducted to determine the influence of Hexetidine on plaque formation, plaque removal and gingivitis is sparse.

The plaque-inhibiting effect of Hexetidine was compared with that of chlorhexidine by Bergenholtz and

Hanstrom in 12 males and 12 females ages 19 to 24 years. Subjects received a prophylaxis and normal oral hygiene was suspended during the course of the study. Groups of subjects rinsed for one minute three times daily with eight 0.4 or 0.14 percent of Hexetidine, or 0.2 percent of chlorhexidine. No inactive control was included. The GI index increased in all groups but was significantly higher in the Hexetidine groups. Significant differences were not detected in the plaque indices. Clearly, in the absence of a negative control, it is difficult to assess the effect, if any, exerted by Hexetidine. Oral lesions and epithelial detachments were noted in five subjects in the Hexetidine groups.

The effect of rinsing three times daily with 0.1 percent solution of Hexetidine on plaque growth over seven days was studied by Williams. A group of 29 volunteers, aged 19 to 58 years, was studied in a double-blind cross-over study in which the rinse was the only oral hygiene carried out. However, because there was such a highly significant cross-over effect, the data were restricted to a parallel study. Plaque regrowth was reduced, at the 95 percent confidence

interval by 42-77 percent. The effect on gingivitis was not studied. Eleven of the volunteers who participated in the study reported some adverse effects; the most common one was loss of taste.

A study by Harper explored the effect of Hexetidine 0.2 percent, and other products also, on plaque regrowth in 21 subjects over four days in the absence of normal oral hygiene. Blind randomized cross-over design was used and saline was included as a control. A 2.5 day "washout" period was used. Hexetidine was significantly more effective than saline in preventing regrowth of plaque. Gingivitis was not measured.

The effect of a 0.2 percent solution of Hexetidine spray on plaque and gingivitis was studied for 28 days in 38 subjects following periodontal surgery. Normal oral hygiene was continued during the study. Spray delivered 1 ml, was used three times daily, and a placebo control was used. Plaque was assessed using Turesky's modification of Quigley-Hein index, and GI of Loe-Silness plus papillary bleeding index were used to assess gingival health. There was

significantly less plaque accumulation in the Hexetidine group and the gingival indices were also lower in the persons receiving Hexetidine.

There have been a number of studies conducted, e.g., Giertsen, Hefti and Huber, Grytten, exploring the effects of Hexetidine in combination with metal ions such as zinc and copper on acid-producing capacity of plaque, plaque accumulation, and strep mutans populations. These studies, usually conducted on three or four subjects using frequent ingestion of sucrose to promote plaque formation, and suspension of oral hygiene, do not contribute significantly to clarifying the effect of Hexetidine on plaque formation and gingivitis.

In summary, therefore, in my opinion, there are questions concerning both the safety and effectiveness of Hexetidine.

CHAIRMAN GENCO: Thank you, Bill. Are there comments or questions from the panel regarding Hexetidine?

(No response.)

Does anyone in the audience want to make a

presentation?

(No response.)

Okay. Thank you. We will proceed then to the soluble pyrophosphate, Dr. Listgarten is going to give this presentation.

DR. LISTGARTEN: Soluble pyrophosphate is a combination of two pyrophosphates and a methylvinyl ether/maleic acid copolymer which must be used together with the pyrophosphates in order to interfere with the inactivation of the pyrophosphates by salivary phophatases and pyrophosphatases. The active ingredients are the pyrophosphates which are used for their ability to interfere with hydroxyapatite crystal formation and, hence, supragingival calculus formation. Pyrophosphates are GRAS ingredients that have been used for a number of years as food additives and as emulsifiers in the manufacturing of cheese in which it may be found in concentrations as high as 3 percent. Pyrophosphates have been incorporated in oral care products such as Colgate's Tartar Control Toothpaste and Tartar Control Formula Mouthwash. Since 1987, 18 million 24 ounce bottles have been distributed without

any report of a serious side effect.

The methylvinyl ether/maleic acid copolymer allows the use of lesser concentrations of the active ingredients by interfering with the action of intraoral phosphatases and pyrophosphatases that tend to enzymatically lyse the P-O-P pyrophosphate bond.

The product is distributed as antitartar agent, a claim that the manufacturer considers to be a cosmetic rather than a drug claim.

Rationale and in vitro tests of efficacy. Exogenous inhibitors of hydroxyapatite crystal growth, such as pyrophosphates, can be applied as mouthrinses and toothpastes to reduce the formation of dental calculus. The efficacy of pyrophosphates as inhibitors of crystal formation have been demonstrated in a number of in vitro experiments using models of spontaneous hydroxyapatite crystal formation or seeded crystal growth. The effectiveness of pyrophosphate formulations is compromised in vivo because of the presence of acid and alkaline phosphatases and pyrophosphatases in saliva that lyse the P-O-P bond of pyrophosphate. To prevent this lysis, a copolymer of methylvinyl ether and maleic

acid, as well as fluoride ions have been used as stabilizers. These agents act by protecting the pyrophosphate from the action of phosphatases. In this manner, it is possible to lower the concentrations of pyrophosphates in the product and still retain their in vivo effectiveness as inhibitors of crystal growth without harming the integrity of tooth surfaces.

Safety: Animal Safety data. TKPP which is the short version of tetrapotassium pyrophosphate and TSPP is what I'm going to call tetrasodium pyrophosphate. Both of these have similar safety spectra. The oral LD_{50} values for mice and rats are approximately 3-4g/kg body weight. Dermal toxicity in rabbits show an LD_{50} value of >7g/kg body weight. Irritation tests to the eye and skin of rabbits show only slight irritation. TSPP is not fetotoxic, teratogenic and at doses of 130-138 mg/kg it has no maternal toxic effects when given to pregnant rats and mice during the 6-15th day of gestation.

Acute oral limit toxicity of Tartar Control Toothpaste in rats. Tartar Control toothpaste formulations contain up to 2 percent TSPP and up to 4.5

percent TKPP. Acute oral limit tests show low acute toxicity with an LD_{50}>5g/kg, and absence of oral mucosal irritation after 28 days of dentifrice administration.

Two similar experiments were conducted in rats. The first experiment tested a toothpaste containing 4.5 percent TKPP and 1.5 percent TSPP. Ten rats were dosed by oral gavage with 5g/kg of dentifrice, i.e., 225 mg/kg of TKPP and 75 mg/kg of TSPP. The rats were monitored for 14 days without any signs of abnormal gain or loss of weight and no anomalies at necropsy.

In the second experiment, a formulation was used with 5 percent TSPP under a similarly designed protocol. The outcome was similar, with no evidence of toxicity prior to or at necropsy.

Oral mucosal irritation study in rats. This experiment used a toothpaste containing 4.5 percent TKPP and 1.5 percent TSPP applied to the oral mucosa of Sprague-Dawley rats for a 28-day period. Clinical monitoring during the experimental period and necropsy results, including histopathological data from various oral tissues showed no adverse effects on any of the tissues.

Experiments with oral rinse formulations. A combination of 3.2 percent pyrophosphate ion, 1 percent copolymer and 0.24 percent sodium fluoride was tested in a rat model for its ability to interfere with calculus formation. The product was applied to 12 rats topically, once a day, five days a week, for three weeks. The test group exhibited reduced calculus scores compared to a placebo group of 12 rats receiving distilled water. The same formulation was also effective in allowing the fluoride in the formulation to exert an anticaries effect.

A formulation that included 1.3 percent pyrophosphate ion, 1.5 percent copolymer and 0.24 percent sodium fluoride was also effective in reducing calculus formation.

Human clinical trials. Mouthrinses containing as little as 1 percent pyrophosphate ion, 0.25 percent copolymer and 0.02 percent sodium fluoride have been effective in inhibiting calculus formation in human clinical trials. Three independent clinical trials carried out under a similar experimental protocol, demonstrate the clinical effectiveness of the combined

ingredients to inhibit calculus formation.

Study 1. Eighty-five subjects completed a six-month clinical trial conducted as a double-blind, parallel study to determine the effect of supragingival calculus formation of a mouthrinse containing 1 percent soluble pyrophosphate and 0.25 percent copolymer, as compared to a placebo without these two ingredients. All subjects received a prophylaxis at baseline and used a fluoridated toothpaste for their twice daily oral hygiene. Subjects rinsed for one minute right after brushing. After six months, the calculus reduction by the test rinse was 37.6 percent compared to the placebo.

Study 2. Seventy-six subjects completed a three-month study with a similar design as that of Study 1 and the same test and control rinses. After three months the test group demonstrated a 31.7 percent reduction in calculus as compared to the control group. No significant adverse effects were reported for either rinse.

Study 3. This study was identical to Study 2, with 80 subjects completing the study. Calculus reduction in the test group was 37.7 percent as compared to the

control group. No adverse effects were reported for either the hard or soft tissues.

Thus, in three independent human clinical trials, the combination of 1 percent pyrophosphate and 0.25 percent copolymer formulated as a rinse proved to be safe and effective in reducing the rate of supragingival calculus formation following an initial prophylaxis.

In conclusion, soluble pyrophosphate oral rinses appear to be safe and are effective in controlling the de novo formation of calculus on freshly cleaned tooth surfaces. Since the studies were carried out primarily for the purpose of controlling supragingival calculus for cosmetic reasons, rather than as an adjunct to controlling plaque and gingivitis, and since no claims are made that could be construed as drug-related claims, it is questionable whether pyrophosphates used in this manner and at these concentrations should be evaluated as drugs.

Note: The above review of pyrophosphate oral rinse is based on the data submitted by Colgate for soluble pyrophosphate dentifrice and soluble pyrophosphate oral rinse.

CHAIRMAN GENCO: Thank you, Dr. Listgarten. Any comments, questions from the panel? Lew?

MR. CANCRO: On the basis of this summary and what I believe to be the intent of the manufacturer, this is strictly a cosmetic effect, it's a cosmetic product, and although I guess it's coming in under the eligibility rule for foreign data, I don't see how it's in the purview of this panel to really come to grips with this. It's a cosmetic product, as you've indicated, Max. So, I'm not sure where this goes, you know. There is no therapeutic end benefit, there is no vote needed in this domain and, hence, why are we doing this?

CHAIRMAN GENCO: Actually, that's a question that could be applied to all of these. This is for information for the FDA. Maybe Bob could give us a little bit more expanded explanation of what this is intended to do for the FDA.

MR. CANCRO: Are you talking about the entire review of these ingredients?

CHAIRMAN GENCO: Yes.

DR. SHERMAN: As I said at the previous

meeting, there's a proposal in the works that would allow these ingredients that were marketed in other countries to be considered in the OTC review. That proposal isn't finalized, so at this point we don't know whether these ingredients will be eligible. But while the panel is meeting, we want the panel's expertise in reviewing these ingredients if, in fact, at a time in the future they are eligible, and that's basically all we're doing. And we are having the panel review all the ingredients that were submitted. If it is concluded that this is, in fact, a cosmetic ingredient, then so be it.

CHAIRMAN GENCO: Does that help?

MR. CANCRO: Well, not entirely because if a manufacturer wanted to market these ingredients in the United States today for the indication of preventing or relieving supragingival calculus, they could. The ingredient is safe. It does work. It has a cosmetic effect. It doesn't need an eligibility rule to do that. So, unless this is being submitted in the context of some drug benefit, then I don't understand the need to do this.

DR. LISTGARTEN: I agree. I didn't feel, after reviewing this, that this really belonged on this panel, but since I was assigned to review it --

(Laughter.)

CHAIRMAN GENCO: I suppose there is a possibility someone may submit it, Lew, for -- with a drug claim, and I think this is almost preemptive.

MR. CANCRO: Thank you.

DR. SHERMAN: We can leave it just at that.

CHAIRMAN GENCO: Okay, thank you. Further comments or questions on this thing?

(No response.)

Okay. The next is a review of chlorhexidine digluconate by Sheila.

DR. McGUIRE-RIGGS: Chlorhexidine digluconate is the active ingredient in two products, eludril and elgydium. Chlorhexidine is bactericidal and effective against Gram-positive, Gram-negative, and yeast organisms. It inhibits plaque formation through a combination of is antimicrobial activities and its adsorption to surfaces in the oral cavity. Eludril is a mouthrinse that contains 0.1 percent chlorhexidine.

Elgydium is a toothpaste with a 4mg per 100g concentration.

Animal Safety Data. The unpublished toxicological expert evaluation assessed the acute toxicity of eludril in mice and rats and the local tolerance of the preparation in rabbits. Symptomatology and toxicity levels seen were due to the alcohol present in the preparations. By virtue of the ocular tolerance index and the primary cutaneous irritation index, the preparations were deemed as non-irritants.

The unpublished animal safety studies on elgydium covered similar areas of toxicity and tolerance. The results were that there is low acute and short-term toxicity, good local tolerance studied at the cutaneous, buccal, dentary, ocular and gastric levels and an absence of undesirable side effects. The preparation also included amidopyrazoline gentisate, an ingredient they later needed to remove.

In two published articles, animal toxicity testing of the active ingredient was reported. Concentration levels were not well identified but the results were that no kind of tumorigenic effect was

found.

Human Safety Data. Two clinical appraisals were conducted in 1978 on eludril. Both studies were limited to populations of children with oro-pharyngeal lesions. In addition to the limited population, the tolerance and safety findings were limited as the main goal of these reports was to show effectiveness of eludril in children.

No human safety data for the finished product elgydium was presented.

Several peer review articles reported on the safety of the active ingredient. The evidence shows it to be safe with no detrimental effects in man over a two-year period other than mainly cosmetic side effects. Poor absorption of chlorhexidine is a factor in its low toxicity. Experiments indicated that mucosal and gingival penetration is minimal, it is poorly absorbed from the GI tract, and when swallowed it is almost completely excreted in the feces and urinary tract. There is some discussion that bacterial resistance to chlorhexidine could occur. One study found a mutation frequency of 0.014 percent when Salmonella typhimurium

was exposed to low concentrations of chlorhexidine.

Staining is the most common side effect when using chlorhexidine products. This occurs mainly on the teeth but also on the tongues of approximately 50 percent of the patients within several days. Rinsing in the evening does decrease the amount of pigmentation. Staining often requires professional removal. No information on calculus formation was presented.

Efficacy Data. Most peer reviewed articles included for consideration were for 0.2 percent concentrations of chlorhexidine. However, Gjermo and Hull showed marked decreases in plaque accumulation and gingivitis with the use of 0.1 percent chlorhexidine. One major concern appeared for the clinical trials submitted for this review. The plaque and gingival indices used to show effectiveness are scales that use 0, 1, 2, 3, and 4. Yet the analyses take the findings to two places behind the decimal. This level of false precision lead me to question the statistical significance found in the intervention population vs. the control population.

Conclusions. Chlorhexidine digluconate is

safe and effective in concentrations currently approved by the FDA for prescription use. The foreign data submitted in large part support the U.S. findings, however, the studies presented do not conclusively support the effectiveness of the low concentrations found in the OTC preparations.

CHAIRMAN GENCO: Thank you. Any comments or questions? Yes?

DR. LISTGARTEN: Could you elaborate on your problem with the statistical analysis. Is it the fact that you are using scores that are analyzed by parametric statistics that's bothering you?

DR. McGUIRE-RIGGS: Well, I believe they did the appropriate statistics, but when they gave a mean for the subjects, these were healthy subjects and the scores were in the 0-1 range, so the clinical significance bothered me. But also that they would -- I don't have the exact number with me, but the control and the intervention populations should have stayed at the scale number, or maybe one decimal. But when they went to .78 or .787, they even went on some to three decimals, it was just that false level of precision.

When they did the statistical significance, I believe if they had stayed at that rounded up level, the significance would not have appeared.

DR. LISTGARTEN: But there was nothing wrong with the statistical analysis other than the fact that --

DR. McGUIRE-RIGGS: Correct.

CHAIRMAN GENCO: Sheila, you mentioned that you are concerned about the concentration levels were not identified. Are you concerned about the two products that you talk about, eludril and the dentifrice -- I don't see it here -- at any rate, the eludril is .1 percent and was that two clinical trials they did look at the efficacy of eludril? So are you concerned that the efficacy of .1 percent is not shown?

DR. McGUIRE-RIGGS: Correct, it's at the .1 percent, and particularly the toothpaste at 4mg per 100g concentration just wasn't there.

CHAIRMAN GENCO: The efficacy.

DR. McGUIRE-RIGGS: The efficacy.

DR. LISTGARTEN: One other question, regarding the toothpaste, did you see anything about the

availability of chlorhexidine in a toothpaste formulation? I recall that one of the problems in formulating chlorhexidine toothpaste was the fact that chlorhexidine was neutralized by some of the other ingredients. Have they solved that problem?

DR. McGUIRE-RIGGS: Well, the only thing they discussed was that there was -- the toothpaste preparation had the amidopyrazoline gentisate which they had to take out, and they weren't very clear why that was dangerous or whether it was because it neutralized it or whether it was a dangerous ingredient to be in the preparation.

CHAIRMAN GENCO: Further comments? Questions?

(No response.)

So the concerns from the foreign data were efficacy at the lower concentration than the .12 which is used in the U.S. and approved for prescription.

DR. McGUIRE-RIGGS: Correct. The data was all very old, and I would suggest that they do some more recent work and really do a sample size big enough to show the effectiveness.

CHAIRMAN GENCO: And the second concern is for

the formulation of the toothpaste. Bill?

DR. BOWEN: Not only the formulation, Bob, but 4mg per 100g is a negligible amount in there, it's not even .0001 percent, it's even less than that.

CHAIRMAN GENCO: Okay. Further comments or questions?

(No response.)

All right. Thank you very much.

Let's proceed on to the next material in the foreign market ingredient, unsaponifiable fraction of corn oil, and Christine will present this.

DR. WU: Insadol is a product developed in France for the treatment of periodontal disease and gingivitis. It has been marketed in France as well as 29 other countries since 1961. It has not been marketed in the United States at any time. The titrated extract of the unsaponifiable fraction of corn oil -- from here on abbreviated as USFCO -- is the active ingredient present in Insadol.

USFCO is supplied in two forms as a systemic agent for the treatment of periodontitis: one form is a drinkable solution which is an anis-flavored, 95

percent ethyl alcohol preparation containing 2.5 percent of the USFCO. Another formulation is in a sugar-coated tablet containing 0.035 g of USFCO. The drinkable solution is used at the dose of one teaspoon diluted in a glass of water to be taken before lunch. The sugar-coated tablets are prescribed at six tablets per day during the initial treatment month, and the maintenance treatment is three tablets or half a teaspoon of the solution per day for two additional months or more.

As presented in Exhibit 18, the USFCO fraction contains, one, an unsaturated hydrogen carbide, squalene, 1 to 2 percent, and traces of saturated hydrocarbons; two, some carotene at 0.1 percent, and some alpha, beta, gamma tocopherols at 1 percent; three, 50 to 70 percent phytosterols at 80 percent sitosterols, 10-20 percent stigmasterols, and less than 5 percent ergosterols, and some sterols of yet undetermined nature; and, four, some substances endowed with estrogen, androgen, and gonadotropic activity.

Safety. The acute toxicity of Insadol raw material, USFCO, in rats and mice was very low, >5g/kg for rats, 10g/kg for mice, 4,000 times the human

1 therapeutic dose. Values for LD_{50} were not given.
2 Subacute toxicity was tested in mice and rats for one
3 month at concentrations of 100 mg/kg and 250 mg/kg
4 respectively. No treatment related mortality was
5 observed. Autopsy showed no macroscopic lesions of the
6 principal organs examined.
7 When administered subchronically and
8 chronically, no signs of toxicity were observed in mice
9 up to 50 mg/kg/day for three months; in rabbits up to
10 150 mg/kg/day for three months; in rats up to 2500
11 mg/kg/day for six months; and in dogs up to 1000
12 mg/kg/day for six months. The material is not
13 teratogenic in rabbits at 50 mg/kg/day, rats at
14 50/mg/kg/day, or mice at 50/mg/kg/day. It did not
15 affect liver or kidney function in rats at doses up to
16 150 mg/kg/day for six months. It did not affect calcium
17 or phosphate metabolism in rat liver in doses of 100
18 mg/kg/day for 40 days.
19 The human exposure to USFCO in the systemic
20 Insadol product has been estimated to be 4 mg/kg/day.
21 Comparing the USFCO doses tested in animal safety
22 studies with the human doses expected from use of a

USFCO containing toothpaste, the safety data appeared to support the use of USFCO at a significantly higher level than that currently present in the Pyoralene toothpaste.

No mutagenicity or oncogenicity studies were conducted. No testing was performed regarding skin, eye and mucosal irritation.

Human Safety. Although USFCO containing products, Insadol, has been used in humans in France as a systemic agent for the improvement of periodontal health, no specific human safety studies have been documented in the submission. As presented in Volume 1 submission, from 1961 to 1984, 1259 patients enrolled in various clinical studies using Insadol products and only five patients reported side effects. Two side effects for the product were reported between 1984 to 1990. As for the USFCO containing Pyoralene toothpaste, which has been marketed in France since 1974, no adverse effects have been reported or received. However, no documentation was provided as to how any of this data was collected and tabulated.

Efficacy. As stated in the cover letter dated June 14, 1991, the Amer and Company requested only the

safety and efficacy of the topically applied toothpaste to be evaluated. In the submission, only two clinical studies were performed to evaluate toothpastes containing USFCO. One was a two-month double-blind trial in 1972 of a gingival paste containing USFCO, Exhibit 32. The study was poorly designed. No information was given as to the placebo and the active ingredient and formulation of the test gingival paste. The inclusion/exclusion criteria for patient selection were not described. No microbiological study was done. The data obtained demonstrated no statistically significant differences in reduction of plaque/gingival index between the treatment and the placebo group.

The second study performed in 1987, Exhibit 33, was a two-month double-blind evaluation of a 1 percent UNISAP-V active ingredient toothpaste versus a placebo. The active ingredient present in this paste was not specified and the chemical formulation of the test paste and placebo were not given. It was not clear if the 1 percent UNISAP-V paste used in this study was identical to the marketed product, Pyoralene toothpaste. In addition to the plaque and gingival index, bleeding

on probing, calculus and stain reduction were monitored. Even though the means of plaque and gingivitis scores were provided in the report, it was not possible to perform accurate statistical analyses of the data. Based on the mean values given, there appeared to be no significant differences in plaque/gingivitis reduction between the treatment and placebo groups. It was stated in the summary of this study, page 14, Exhibit 33, that "additional evaluation of the active ingredient at higher level needs to be performed and that future study with longer duration than two months is warranted". No microbiological studies were performed regarding the effect of test paste on oral microflora.

Conclusion. A majority of the safety and efficacy data submitted for the review was more than 20 years old, and most of these were related to the product Insadol. No additional data since 1981 has been provided.

As provided in the exhibit, USFCO is a mixture of a variety of components including vitamins, sterols, estrogens and other non-identified substances. Although it was stated that, in Volume 1, page 10, the USFCO was

standardized to assure reproducibility from batch-to-batch, no data was provided regarding the procedures used for chemical and physical characterization of the material. The modes of action of USFCO have not been clearly elucidated. Whether it poses antimicrobial activity is not known. It was stated in Exhibit 19, in 1967 by Laboratories Laroche Navarron, that "the therapeutic action of USFCO cannot be explained by its unknown constituents, but is possible that what is useful is not one special constituent but a synergy". Its possible anti-inflammatory activity has been suggested.

As stated in the submission materials, Insadol is used in France as a systemic agent for the treatment of periodontal disease. It is not clear as to whether USFCO should be classified as a therapeutic drug or food supplement. In either case, it is not the responsibility nor the function of the Subcommittee to review safety/efficacy data for these types of products.

Although the available animal safety data seemed to be support the use of USFCO at a significantly higher level than that currently present in the

Pyoralene toothpaste, additional safety studies need to be performed to substantiate the safe use of a toothpaste containing USFCO in human.

Data obtained from the two clinical trials in 1972 and 1987 were inadequate and did not provide sufficient evidence to substantiate any anti-plaque/gingivitis efficacy of the USFCO or the topically applied toothpaste containing such ingredient.

CHAIRMAN GENCO: Thank you, Christine. Any comments, questions?

(No response.)

Okay. I hope that was useful.

We will go to Bromchlorophene. Gene Savitt will present this.

DR. SAVITT: Bromchlorophene has been marketed in Europe, South America, Asia and Australia since 1960. The ingredient is marketed in both toothpastes and mouthrinses at concentrations up to 0.5 percent. The submitted documents commonly described bromchlorophene as a preservative.

Safety. Most of the limited documentation concerned safety testing. These tests included several

LD_{50} studies examining lethal concentrations using a variety of administration techniques. The LD_{50} results indicated that the concentration of bromchlorophene showed lethal doses at 8 g/kg orally -- this is rats -- 10 g/kg percutaneously, and 500 mg/kg intraperitoneally.

Acute toxicity studies showed no toxic effects below 250 mg/kg administered orally. Above these levels, toxic symptoms included sedation, lethargy, dyspnea and ataxia.

Short-term inhalation toxicity study showed only minor and reversible effects.

Draize test study in rabbits displayed minimal conjunctival reactions, and only slightly greater skin irritation at a concentration of 50 percent w/v.

No human phototoxic effects on skin were found using a 2 percent bromchlorophene solution dissolved in alcohol.

An Ames test found no mutagenic effect.

The submitted absorption and excretion study showed bromchlorophene is concentrated in the liver when administered orally and is excreted after 24 hours.

The safety tests appeared to be routine and

appropriately conducted. Numbers of test subjects appeared to be similar to other safety studies examining other products. While additional and more extensive safety testing might be necessary following a review by a qualified toxicologist, the safety studies appeared in keeping with products considered safe as previously reviewed by this committee.

There were three studies that examined efficacy. All three studies had significant flaws making interpretation difficult or impossible.

One study of ten weeks duration divided 110 children into four groups; two test and two control groups. One test and one control group had orthodontic treatment while the other two groups did not. The test groups received a paste with 0.05 percent bromchlorophene. The control groups received a paste without the bromchlorophene. None of the pastes contained fluoride. The precise formulation of the pastes were not described. Gingivitis was assessed using the PMA gingival index. Plaque levels were measured using an oral hygiene index with disclosing solution. No data other than final percentages of

gingivitis and plaque reduction were given. No statistical analysis was offered nor were standard deviation and other basic information available.

The authors suggested that the group receiving the test paste undergoing orthodontic treatment showed noticeable improvement in gingivitis -- 76 percent of subjects had reduced gingivitis -- compared with the control orthodontic group -- 40 percent of subjects showed reduction in gingivitis. The non-orthodontically treated groups also showed gingivitis reduction -- 64 percent of test subjects had less gingivitis compared to 52 percent of control subjects. However, without proper data presentation and statistical analysis as well as much more extensive description of methods, no firm conclusions could be reached. It is also unclear whether a non-fluoride paste would be appropriate and acceptable for introduction into the United States.

The next efficacy study examined bromchlorophene at 0.05 percent, combined with an anti-inflammatory agent, allantoin at 0.2 percent, plant extracts and alcohol. There were many confusing and poorly described aspects to this study. For example, no

numbers were presented. It was unclear how many subjects were even in the study. Methods were inconsistent. The rinse was apparently administered both as a spray and as a rinse at varying frequencies using vaguely described criteria. No measurements were taken or at least not described. Concentrations of ingredients were unknown or not listed. No controls appear to have been used. As a result, no interpretation of the experiment is appropriate. A side study of light microscopic stained smears was also poorly described and the authors concluded that the number of samples were too small to permit interpretation.

The final efficacy study examined the effect of a paste with monofluorophosphate combined with bromchlorophene compared to a paste without either ingredient. Concentrations of test ingredients were not given. The study was conducted on 1245 children over two years and examined decayed, missing teeth and filled surfaces as a measure of efficacy. Since the control paste did not contain either fluoride or bromchlorophene, the study conclusions that indicated a

significant reduction in DFMS scores for the test group provides only additional data to the already extensive pool of information on the anticaries effects of fluoride. It is impossible to determine whether the addition of bromchlorophene had any effects on caries from the data presented.

The efficacy tests on bromchlorophene were inadequate to suggest any value for the ingredient. There were no properly controlled or accurately described studies to indicate positively or negatively if bromchlorophene is a potentially useful drug in the treatment of caries or periodontal diseases.

CHAIRMAN GENCO: Thank you very much, Dr. Savitt. Any comments or questions? Yes, Lew?

MR. CANCRO: I would like to ask the FDA advisors with us today about the procedural aspects of this aspect of the review. Summaries have been written on the ingredients. Their eligibility will be declared at some point by the FDA and, consequently, what happens, are the panel members polled retrospectively? Does it go to NDAC if the ingredient is found to be eligible? And if eligible, can it be marketed in this

country while the manufacturers are pursuing sufficient evidence to establish efficacy? I'd like some procedural understanding of this.

MS. KATZ: I'm not sure at this point I can really give you a comment to all the questions that you're asking. Part of the reason for that is that this gets tied into the foreign marketing and that at this point in time there is no official policy from the Agency. So, as to how this information will be used and whether or not it will formally come back again, whether the panel will be reconvened, whether there will be another panel that will address these issues in the future, I can't answer for you.

The reason, again, why it was brought to you at this point in time was just to get sort of a feeling as to some of the requests that we have received, just to kind of, in a sense in our own minds, think of ways that we might be able to categorize or not categorize them. This was purely informational only and was not intended to go into the document that is being worked on at this point in time. And, again, as to how the Agency will deal with this, that will remain to be seen.

MR. CANCRO: So these reports will not become part of the advance Notice of Proposed Rulemaking?

MS. KATZ: No, it will not. It will be a part of the transcript, but that's as far as it will go at this point in time.

CHAIRMAN GENCO: Would you come up to the microphone, please, and identify yourself for the record.

DR. OKARMA: I'm Paul Okarma, Colgate-Palmolive Company. Sometimes I'm clueless as far as what's going on. And we were discussing this morning these submissions in the broad context of foreign marketing data and, as Professor Listgarten was reading the soluble pyrophosphate submission, I was wondering, boy, I wonder who submitted that, that sounds a lot like our data.

Well, that was our data, and that was data -- what's even worse is that was a submission I wrote in 1991. So that was our data and, as Lew pointed out, that product is marketed -- both those products, the rinse and the toothpaste, are marketed in the United States, both the tartar control rinse and the tartar

control toothpaste. So, that submission, the soluble pyrophosphate submission, we request be taken out of any discussion of foreign marketing data and perhaps included in the panel report in a separate section on perhaps something titled Panel Review of Submissions Which the Panel Have Determined Are Cosmetic In Nature, that being supragingival calculus. Thank you, Mr. Chairman.

CHAIRMAN GENCO: I guess we're going to have to look into that, but it appears that we decided, it seems years ago -- might even have been decades -- that we wouldn't deal with cosmetic claims. But we'll have to look into that. I will take your comment under advisement.

DR. OKARMA: Thank you, Mr. Chairman.

DR. SAVITT: Just a note of clarification. Many years ago the question was presented to us whether calculus should be considered -- or anti-calculus claim -- should be considered drug versus cosmetic, and I suspect that when the original request for information went out that since we hadn't met, we hadn't decided on this, that calculus was still a possible drug claim.

CHAIRMAN GENCO: I think that accurately describes the history.

DR. OKARMA: The Federal Register Notice in September of 1990 listed this as a call for data for plaque and plaque-related claims, and then parenthetical after that, as one of the other example claims, was listed tartar, and that's the reason we did submit the pyrophosphate information on tartar. Thank you, Mr. Chairman.

CHAIRMAN GENCO: Thank you. Further comments, questions?

(No response.)

I'd like to thank Rhonda for cranking up the air conditioner. The temperature in here is now 47.5 degrees F., which is appropriate for that last discussion. I notice that nobody fell asleep.

(Laughter.)

Well, we're ahead of time, and in fairness to Dr. Soller and others who are going to present at one o'clock, what we'll do is break now and then resume our open discussion, open public hearing, on the final formulation testing with Dr. Soller and Dr. Barnett. So

we'll see you back here at one o'clock. Thank you very much.

(Whereupon, at 11:40 a.m., the luncheon recess was taken.)

AFTERNOON SESSION

(1:00 p.m.)

CHAIRMAN GENCO: We're going to discuss final formulation testing this afternoon, and we'll have two presentations, the first by Dr. William Soller, who is Senior Vice President, NDMA, and he's going to present some material on final formulation testing under the OTC review process. Dr. Soller.

DR. SOLLER: Thank you, Dr. Genco. Dr. Genco, members of the subcommittee, it's a pleasure to be here. I'm Dr. Bill Soller, Senior Vice President and Director of Science and Technology for the NonPrescription Drug Manufacturers Association, and I'm here representing the NDMA and CTFA, Cosmetic, Toiletry, and Fragrance Association, Joint Oral Care Task Group, and we'd like to share our views on final formulation testing under the OTC review. And I understand our comments were sent to you last week, and you received those. I'll be summarizing those comments. And I've also had the overheads that I'll be using today handed out to you.

At the last subcommittee meeting, the request that we understand to companies from the subcommittee

was to provide recommendations for performance testing on those Category I ingredients recommended for anti-plaque and anti-gingivitis use. And that was to ensure that a different formulation that might be made by a different manufacturer, a different formulation than the one reviewed by the subcommittee, will have a "reasonable expectation of effectiveness" of the type claimed, and these words taken from the definition of "effectiveness" within the OTC review.

So our comments are in four parts. Some background comments on the purpose of the OTC review; by way of providing the foundation for a description of FDA's interrelated system for assuring OTC product quality; and then I will have short comments on elements of final formulation testing, what other panels considered conceptually as they made these sorts of ingredient-by-ingredient decisions; and then our recommendations.

Now, in the OTC area, there are two routes to market -- the OTC NDA, or new drug application route, and the OTC monograph or the OTC review route that was started in 1972.

The OTC NDA route requires that every product that has a new drug application must have preapproval by FDA prior to marketing. That is not the case for ingredients that are in products that are marketed pursuant to the OTC review. And the reason for that is that in 1972 when FDA initiated the OTC review, there were some 150,000 different product types and sizes on the market. And for FDA to then have to do an approval on each and every one of those product types and sizes would simply have been a massive and incomprehensible task. And as a result, FDA created an active ingredient review, and they set in place several checks and balances that would ensure that an OTC product that was marketed pursuant to the OTC review could be marketed without preapproval.

Now, this means that any manufacturer which complies with FDA's "rules of the road" for packaging, labeling, and manufacturing can pick an ingredient from FDA's list of accepted Category I ingredients that appear in final monographs, and can go to market without a formal preapproval from FDA. It doesn't mean that the product is not appropriately tested, and that's what I'm

here to talk to you about. But this system that I'll describe is a very efficient system. It's a very successful system that has 25 years experience, and it is actually pro-consumer because it fosters market competition.

So the purpose of the OTC, the OTC monographs, is to define, as needed -- those are key words, "as needed" -- the appropriate level of specifications for final formulation testing so that there is a reasonable expectation that the product produced by the manufacturer is substantially comparable to the formulation that was reviewed by the OTC Advisory Panel in creating the final monograph. And I should say that whether it is NDA or monograph, that both system create products that are essentially comparable in terms of their safety, their effectiveness, and their quality, as they are marketed on the over-the-counter marketplace.

Now, you should know that there is a very solid foundation of extensive testing of OTC final formulations, whether they are NDA or monograph, and this occurs through FDA's interrelated system for assuring product quality.

So the question really before you today is what, if any -- key words, "if any" -- additional tests are needed over and above this established system that is used for products that are marketed pursuant to the OTC review.

This is a schematic showing FDA's interrelated system for assuring product quality. This system is essentially an interconnected matrix of checks and balances that assures that any manufacturer at this end down here can produce a safe, effective, and quality product that is substantially comparable to the original formulation reviewed by the FDA Advisory Committee and used in its deliberation to create the final monograph. For example, if you look at stannous fluoride, and I'll comment on this later, but you looked at that original formulation, you reviewed it, and you looked at the clinicals, and you're basing that information to create the proposed monograph. After a final monograph is created, then any manufacturer using this interrelated system would then be able to market a safe, effective, and quality product. And what we'll talk about are these different components -- the OTC monographs, the United

States Pharmacopeia National Formulary Monographs, current good manufacturing practices -- abbreviated cGMPs -- and then what I call the "SALT Treaty", FDA's inspectional authority, trust but verify. Let's take these one at a time.

The OTC monographs. All actives must meet USP/NF monograph specifications as part of FDA's system for final monographs. And I haven't included here the specifications that have to do with labeling, the dosage and amount for dosage unit, and those sorts of considerations that you've gone through, I'm talking more about the technical aspects of the monograph, and we'll talk in a moment about the USP/NF.

But in addition, various panels have looked at their specific ingredients within various categories and stated that there should be certain additional final formulation testing. Now, as you look across all these monographs, these final formulation specifications vary and they are case-specific. For example, there is no specification in the cough/cold monograph -- that was really the panel report in the proposed monograph -- that pseudoephedrine or dextromethorphin or

chlorocopyrimin or any of these cough/cold products should have any additional final formulation testing. The USP monograph that was set up required certain dissolution testing and identity and assay requirements that I'll show you in a moment, that are used for various physiochemical characterizations of the ingredients.

But if we were to take aspirin, the panel on internal analgesics stated that there should be a disintegration/dissolution test that should be set up in USP and used as a requirement for a Category I ingredient to be marketed in a product that was in conformance with the OTC review. So the panel report stipulated that the aspirin, acetaminophen as well and other salicylates, must meet the USP disintegration/dissolution for solid dosage forms.

The antacid panel, which was the first to complete its report, created an acid-neutralizing capacity test which was then modified and adopted by USP, but here again it's an additional piece of final formulation that goes over and above the USP monographs.

And for fluoride, the oral care panel

specified that there needed to be certain additional in vitro and in vivo tests. For fluoride, it is either the enamel solubility reduction test or the fluoride uptake by enamel, either one of those in vitro, plus an in vivo rat caries model that would be looked at. But I will tell you that there are also ophthalmic emollients, et cetera, that would be perhaps up in this part of the list where there is no additional final formulation testing.

So, again, back to that original question that I showed in the earlier slide. The question is, what, if any, additional final formulation testing is needed for these particular ingredients?

Now, the second component -- we looked at the OTC monographs -- are the USP, United States Pharmacopeia National Formulary monographs, that provide requirements for strength, quality, purity, identity and potency of both raw materials and finished dosage forms across a host of different types of tests from identity, content uniformity, assay, pH, specific gravity, disintegration, dissolution, packaging, storage, reference standards, the whole gamut, and this is not a

totally inclusive list, there are many other tests that were required, but they are there ingredient-specific. And in fact, if you were to look at the identity and the requirements for the percent that's allowed, you might see for pseudoephedrine 97-102 percent, somewhere in that range -- don't quote me exactly on those figures; for aspirin 95-105; certain other ingredients 95-115 -- all to very formulation-specific tests that were created between USP and the manufacturers and USP's Revision Committee and its equivalent of the Federal Register for public comment, the Pharmacopeial Forum, to create very ingredient-specific standards that would be applied and therefore are linked to the OTC monographs.

The third component -- the OTC monographs, the USP monographs -- and now current Good Manufacturing Practices, or cGMPs, under 330.1(a) of the Code of Federal Regulations, all OTC drugs marketed pursuant to the OTC review must be manufactured per current Good Manufacturing Practices.

These cGMPs and their companion guidance and guidelines cover all aspects of manufacturing, packaging labeling, from storage and handling of raw materials to

production and process controls, analytical testing, specifications for facilities, records, consumer reports, and the list goes on. Truly, if you saw the full stack of guidances that are associated here, it is absolutely daunting the number of specifications and tests that manufacturers typically go through to produce a quality product in the U.S. pharmaceutical distribution system.

And then the SALT Treaty, FDA's inspection authority, which is "we trust that you're going to do it, but we want to verify that, in fact, you're going to do it". Under Section 704 of the Food, Drug and Cosmetic Act, FDA at reasonable times and in a reasonable manner and within reasonable limits, may enter a facility or a vehicle that's being used to hold/transport, drugs, devices, foods, or cosmetics. They can look at records, and typically inspectors look at records to determine that an OTC drug that is being marketed pursuant, for example, to the OTC review, is being produced in a manner that is consistent with the OTC monographs and the USP/NF monographs as well, as well as current Good Manufacturing Practices.

So, back to our schematic here, here is the original formulation -- I used stannous fluoride earlier -- being reviewed by the FDA Advisory Committee and creating a proposed monograph that eventually will be a final monograph, having to comply with USP/NF monograph, and certainly current Good Manufacturing Practices. I've listed here the types of tests. Of course, the first three here are related to labeling, the USP monograph requirement I just mentioned, and whatever additional in vitro or in vivo formulation testing, if any, that might be required. Physiochemical testing, principally over on the USP/NF monograph side, and then the analytical and process controls for manufacturing and packaging, creating this interrelated matrix for a very solid, efficient, and successful system for producing high quality products. And, again, the SALT Treaty-FDA inspections to allow any manufacturer, after a final monograph, to pick from the list of Category I, anti-platelet, anti-gingivitis products that you are creating, and create a product that is substantially comparable to that original formulation.

Now, as these various panels considered how

are we going to think about final formulation testing -- the basic principle is really ingredient-by-ingredient and let's think about what the specific formulation differences are because, truly, one chemical is not like another necessarily when you now get it into a formulation mode, but there were also three additional principles of strength, availability and activity. Strength or concentration, for example, if it's a liquid, does the final dosage form meet the specifications of the USP and OTC monographs?

In terms of availability, if it's there in terms of the amount that you say it is in the tablet, is it available?

What additional tests, if any, are needed to ensure a reasonable expectation of availability? And the same question in terms of a reasonable expectation of activity.

Now, pulling this together with some examples, if we were to think about an ophthalmic emollient, for example, just defining that it's there and in terms of its concentration is pretty much what that USP monograph looks at. But if you were thinking now in terms of

availability -- take aspirin in the disintegration/dissolution test in terms of demonstrating that, in fact, you were able to pick up aspirin from the fluid once, in the paddle test, it has been disintegrated and actually the pieces have dissolved.

And then in terms of activity for that aspirin, there is not a requirement for bioavailability/bioequivalent study because of what is known by the formulation when it behaves in a certain way in that in vitro disintegration/dissolution test, so no human additional testing.

But let's take antacid, which is a nuance where you have the acid neutralizing capacity test so that the antacid needs to dissolve in order to neutralize the acid, but by demonstrating the pH change, you are also demonstrating activity, and that's a surrogate for what happens in the stomach.

And if we were then to look at fluoride, of course, it's a requirement for an anticaries product to state the amount of available fluoride on the label, so that needs to be tested, and fluoride ion is a part of

the requirement for the USP monograph on, for example, stannous fluoride.

In terms of activity, the panel stated, yeah, we need to do a little bit more in this particular case. We want to have the enamel solubility reduction test. We want to have fluoride uptake by enamel, and do one of those two in vitro and, in addition, we want an in vivo rat caries. So there we have the availability and the activity, but in no case, at least that I'm aware of to date, has there been a requirement for a specific human clinical trial, just by way of historical note here.

So, by way of summarizing, we have these four components, the monographs and the cGMPs and the FDA inspection, that create this interrelated system that does not create a barrier to commerce. It defines an efficient and predictable means to produce quality products at reasonable costs. And what has been done by panels in the past is to take a case-by-case approach using strength, availability and activity as the conceptual parameters to define the scope and extent of additional specifications for final formulation testing, if any, in OTC monographs.

So, our recommendations, final formulation testing for products under the monographs should be considered on an ingredient-by-ingredient, weight-of-the-evidence basis, for each active ingredient or combination of ingredients, from in vitro to in vivo studies, e.g., ranging from animal to human clinical testing, if any.

Now, you've probably figured out that this task group hasn't always had a consistent view, and we've had majority-minority views. I can tell you that it is, in some sense, mixed here, and that is the schematic that I showed you in terms of how panels have approached this particular issue, there is no question that the industry feels very strongly that there has been a pattern established, and very good and workable one, through the monograph system to review it in the conceptual framework that I just gave you.

The companies believe -- and maybe we could have that last slide -- and we worked hard on this wording -- is that it should be ingredient-by-ingredient, and it might range from in vitro to in vivo studies, ranging from animal to human clinicals, if any.

And the reason that it's important to consider this on an ingredient-by-ingredient basis is that these companies have extensive experience with the formulations, and they can provide you with the ins and outs and the heartaches and the successes with the particular formulations.

But let's look at the three ingredients that you've recommended for Category I status -- stannous fluoride, CPC, and the fixed combination. And just by way of comment to emphasize the point as to why they should be considered on an ingredient-by-ingredient basis and why also as you do this to consider what the companies have to say about their particular products, CPC and the fixed combination are not used for caries prevention, they don't have fluoride in them. Stannous fluoride is.

Now, consider stannous fluoride. If we were to look at the USP monograph, for example, for stannous fluoride, you would see that here it contains not less than 71 percent of stannous, not less than 22 percent, more than 25 for fluoride, and then it goes through and I believe down here there's an assay for stannous ion

and a requirement, for example, for assay of fluoride and also assay for stannous ion content.

My only point for bringing this up is that I have mentioned that in the caries monograph, there is a requirement for fluoride containing active ingredients to have not only a requirement for the USP monograph and meet those, but also to have in vitro testing in terms of enamel, solubility reduction, or chloride uptake by enamel, one of those two, plus an in vivo rat caries model.

Now, if fluoride is important for the anti-plaque/anti-gingivitis, or the anti-gingivitis effect rather, or stannous fluoride, or stannous ion is important, probably it's a mix of two and there's a lot of emphasis that the stannous ion is important. Well, here is a monograph that specifies the stannous ion content. Maybe, for example, the additional point here is to specify a tighter limit for stannous ion. But given that you have, just by way of example, a stannous fluoride ingredient that now has a substantial amount of final formulation testing already applied to it, the question I would have, in order to ensure that you have

a robust quality product, truly, how much more do you need to go? And I'm not going to answer that question, but what I'm trying to leave you with is the need to recognize that these ingredients are different. They are handled differently. We've got liquid formulations. We've got semi-solids. We've got a different historical base in terms of what the final formulation testing is, and that it is appropriate to listen to the companies in terms of what their experience is on these specific formulations. Thank you very much.

CHAIRMAN GENCO: Thank you, Dr. Soller. Are there any comments or questions of Dr. Soller from the panel? Bill?

DR. BOWEN: Dr. Soller, could you elaborate on what you mean by weight of the evidence basis?

DR. SOLLER: I will, and I think some of the things that I was trying to get at at the end where you have a fair amount of additional final formulation testing -- I'm answering your question by way of example -- with stannous fluoride, where you have this in vitro, you've got an in vivo, you've got USP specifications for stannous ion and for fluoride ion, you have to label for

fluoride ion, and you have considerable amount of final formulation testing that's going on there, that doesn't go on, for example, through CPC. And given that weight, what more do you truly need in terms of trying to define a robust quality product? And you might make a different decision depending upon which of these three ingredients that you're looking at.

And I will add that if there are Category III ingredients, it is quite possible that the kind of formulation testing that might be done on those in the future, as might be put through the review and comment procedure as we get to a final monograph, might be different than what you've come up with today for these other three ingredients. So, I'm really getting at a case-by-case. You might have more than one test, and you might say, okay, this isn't a human clinical trial as we looked at to begin with, but I've got enough information here to be able to say that I have a reasonable expectation that the product that will be produced by this manufacturer will be substantially comparable to the one I reviewed in creating this particular -- I, Dr. Bowen reviewed -- in creating this

final monograph.

CHAIRMAN GENCO: Further comments, questions?

(No response.)

Thank you very much.

DR. SOLLER: Thank you.

CHAIRMAN GENCO: I'll ask Dr. Mike Barnett now to come up, from Warner-Lambert, and he's going to discuss final formulation testing for mouthrinses containing the fixed combination of four essential oils.

DR. BARNETT: Thank you very much, Dr. Genco. For the record, my name is Dr. Michael Barnett, and I am Senior Director of Dental Affairs, in the Worldwide Consumer Healthcare Research and Development Division of the Warner-Lambert Company. I appreciate the opportunity to speak to you this afternoon on the subject of final formulation testing for mouthrinse products containing the fixed combination of four essential oils found in Listerine Antiseptic.

There are numerous data which demonstrate that the activity of antimicrobial ingredients can be adversely affected by excipients in a formulation. And in fact, this subcommittee has encountered such

instances in the course of its ingredient review.

On the basis of this experience, this committee concluded that final formulation testing should be required to demonstrate that the activity of active ingredients in products marketed under the OTC Drug Monograph has not been compromised by new vehicle formulations. Warner-Lambert agrees with this conclusion, and I will briefly discuss testing requirements we are proposing to assure that new mouthrinse products containing the Listerine fixed combination of four essential oils have been formulated to provide a level of effectiveness comparable to that of the clinically tested Listerine formulation.

The effectiveness of a mouthrinse containing the fixed combination of essential oils in reducing supragingival plaque and gingivitis has been demonstrated in numerous long-term clinical trials. The mechanism of action by which the fixed combination exerts its effects if based on its antimicrobial activity, which has been demonstrated in both in vitro and in vivo studies.

The final formulation tests we are proposing

for the fixed combination of four essential oils are based on the following premise: A combination of in vitro and in vivo tests should be required since in vitro tests alone, while able to confirm the spectrum of antimicrobial activity of a given formulation, are not necessarily indicative of the clinical antiplaque/antigingivitis activity of the formulation.

Each study, therefore, has its own rational and objective. The objective of the in vitro study is to confirm the spectrum of activity of the formulation against a panel of representative ATCC typed strains as well as against wild-type organisms obtained from the oral cavity. The objective of the in vivo study is to confirm the effectiveness of the formulation against an actual dental plaque biofilm and the clinical endpoint, gingivitis, in the presence of saliva and other factors in the mouth which might interfere with the activity of the active ingredient.

The in vitro and in vivo tests that we are proposing for the fixed combination of essential oils in a mouthrinse formulation are, respectively, an in vitro kill time determination, also referred to as a kill

kinetics or Bahn test, and a short-term clinical trial based on the well known experimental gingivitis model. We have included a representative protocol for each of these tests with our submission to the subcommittee, so I will only mention some aspects of these tests here.

The kill time determination is a recognized method by which to assess the antimicrobial effectiveness of oral formulations and has been recommended, for example, as early as 1982 during the development of monographs for OTC oral healthcare drug products.

The assay evaluates the extent evaluates the extent to which an antimicrobial mouthrinse formulation kills standard cultures of microorganisms in the presence of serum under defined conditions of time and temperature.

Three ATCC strains have been specified for evaluation, namely, Actinomyces viscosus, ATCC No. 19246; Candida albicans, ATCC No. 18804; and Streptococcus mutans, ATCC No. 25175. In addition to these, we recommend the inclusion of a Gram-negative organism, Fusobacterium nucleatum, ATCC No. 10953, as

well as wild-type organisms obtained from saliva. The latter are included because wild-type organisms have been shown to have an increased resistance to killing compared to stock cultures.

The kill kinetics assay will compare the new formulation to the clinically tested formulation containing the identical fixed combination of four essential oils, that is, Listerine antiseptic, and a sterile-water negative control. Testing should be conducted with an exposure time of 30 seconds in the presence of serum as a source of exogenous protein in order to correspond more closely to actual use conditions for the essential oil-containing mouthrinse. Details of this test and its interpretation are contained in the protocol included with our submission. In the interest of time, I will not reiterate them here.

With respect to the in vivo test, the necessity for this component in final formulation testing is based on the finding that laboratory results are not necessarily predictive of how a formulation containing the fixed combination of four essential oils will perform in the conditions of the oral cavity.

Clearly, the conditions under which these tests are conducted differ considerably. In the case of kill time determination, the active ingredients interact with planktonic organisms while under actual use conditions it is important that the formulation have the ability to rapidly penetrate into the plaque biofilm and that the active agents not be adversely affected by saliva or other factors.

Therefore, the clinical test complements the laboratory test and confirms that antiplaque/antigingivitis activity of the essential oils has been maintained in the new formulation.

Insofar as this subcommittee's Category I recommendation for the fixed combination of essential oils was based on both antiplaque and antigingivitis effectiveness, we believe that the in vivo test should evaluate both these parameters.

The test we are recommending is a short-term study based on the classic experimental gingivitis model. Studies using protocol designs based on this model have been frequently used to assess the inherent antiplaque and antigingivitis activities of different

mouthrinse formulations, independent of the variable introduced by mechanical plaque control procedures.

Some of the studies have been conducted on mouthrinses containing the fixed combination of essential oils and have confirmed the ability of this model to demonstrate plaque/gingivitis effectiveness when compared to a negative control. These include published studies which were included in the 1991 submission to this subcommittee.

Three groups should be included in this study -- Listerine Antiseptic positive control, the new formulation, and an appropriate negative control. The study should be of at least two weeks duration, and comply with the statistically requirements to demonstrate a formulation to be "at least as good as" another formulation as discussed by Kingman. Again, since the details are included in the protocol we submitted, I will not reiterate them here in the interest of time.

In conclusion, Warner-Lambert agrees with this subcommittee concerning the need for final formulation testing and, in response to your request for ingredient-

specific test, proposes the following: Final formulation testing for the fixed combination of essential oils should include both an in vitro and an in vivo component to confirm the antimicrobial spectrum and clinical activity of the new formulation respectively as compared to the Listerine Antiseptic standards.

Warner-Lambert proposes the kill kinetics determination and a short-term plaque/gingivitis based on the experimental gingivitis model to achieve the goals of final formulation testing in an efficient, cost-effective manner.

I'd like to thank you for your attention, and will be pleased, or one of my colleagues will be pleased, to respond to any questions you might have.

CHAIRMAN GENCO: Thank you, Dr. Barnett. I'd like to ask a question. If it's necessary to do the short-term experimental gingivitis human study, and that's based upon your observation and the literature which shows no straightforward correlation between in vitro and in vivo, why do you recommend doing in vitro at all?

DR. BARNETT: Well, I think the first step --

obviously, it's simpler, in a sense, to do the in vitro test. So, I would think that unless the formulation passed the in vitro test, it would not make sense to go ahead and attempt to test it in vivo because the probability of effectiveness is extremely low.

I think the second point is because the in vitro test confirms that you've retained your spectrum of activity -- and it may be, for example, that you would want to include more organisms -- so that, as you know, part of the assessments of these things is what effect these antimicrobial formulations will have on the oral flora with time.

I think what the in vitro test does is it gives you some information about the effect of the formulation on very specific organisms that might not be reflected in a relatively short-term plaque/gingivitis model. So I think there are two rationales, two reasons why you would do the in vitro test as well.

CHAIRMAN GENCO: Thank you. Bill?

DR. BOWEN: Are there any appropriate panel models that you're aware of that could be using these gingivitis studies?

DR. BARNETT: I'm not aware of any that would be as effective, quite frankly, Bill, as the human model. You know, it's hard to get -- obviously, this sounds trial -- but it's hard to get the animals to rinse. The plaque biofilms may be a bit different, and I think that it would not be a reasonable surrogate for the human trials.

CHAIRMAN GENCO: Just to follow up on that, Bill, isn't there data, though, that shows that, let's say, the beagle dog spontaneous gingivitis resolution model is a reasonable surrogate -- reasonably predictive for the human effects?

DR. BARNETT: I can tell you, Bob, again, we're talking about ingredients, and in terms of essential oils I'm not aware, quite frankly, of any animal model that one can substitute. I think you might be quite right with respect to chlorhexidine, for example.

CHAIRMAN GENCO: Is it because it hasn't been tested, or because it's been tested and doesn't correlate well with the essential oils?

DR. BARNETT: We've really not looked at all

the models.

CHAIRMAN GENCO: So there is no evidence that would support using the beagle dog or any other animal as predicting the essential oil fixed combination?

DR. BARNETT: Well, basically, as I said, there has been a fair bit of experience testing essential oils in human short-term models, but not animal models.

CHAIRMAN GENCO: Thank you. Max?

DR. LISTGARTEN: If you can do it humans, don't do it in dogs, which I think is probably a good guideline.

(Laughter.)

The question I had had to do with the Loe and Silness model of experimental gingivitis. One part of the model is you stop brushing your teeth for 21 days and let plaque and gingivitis develop. The second part of the model is after 21 days you have plaque and gingivitis, then you reinstitute therapy and plaque and gingivitis disappear. Do you visualize doing both arms of this study, or just the first arm, or maybe just the second arm?

DR. BARNETT: No. The way these are typically done -- and, in fact, I think we've used two-week time periods more frequently than three weeks, Max -- but at the end of the two-week period, all the subjects receive a dental prophylaxis, and then of course they go back to doing whatever oral hygiene procedures they did. So the trial then is effectively ended at that point.

DR. LISTGARTEN: So you don't visualize testing for the ability of the combination to improve on existing plaque and gingivitis?

DR. BARNETT: No. I think the question is what we are really trying to accomplish here, and the purpose is to demonstrate comparability of formulations. And I think the simplest way to do that is a two-week trial. That's a fundamental question that's being asked.

CHAIRMAN GENCO: To follow up on that, is there any evidence that you know of, either with your product or any others, which shows the difference between the effect on buildup of plaque and induction of gingivitis and experimental gingivitis model as compared to reduction of spontaneous gingivitis in humans? Are

there any agents that do one and not the other? I mean, you're asking --

DR. BARNETT: Well, I can speak for our agent, and we have tested, as you know, in six-month clinical trials looking at both models, a reduction of existing and inhibition, and it's been shown to be effective in both cases. I really can't speak to the literature on all the other agents.

CHAIRMAN GENCO: Further comments, questions?

DR. SAXE: Just as sort of a cautionary note again, Mike, and I'm certainly glad to hear that you're enthusiastic about final formulation testing when there would be changes in the product, but switching over to the experimental gingivitis model, first of all, of having human beings volunteer, and granted that one with adequate inducements could bring together a study population not to brush for two weeks but to use an agent in question, is that one knows that there is going to be quite a difference -- certainly, you could document easily, as Dr. Genco pointed out, in the plaque accumulation over that period of time, some people will accumulate large amounts of plaque, some

much lesser amounts, so you already have a variance in that population. And the question then becomes one has to consider how one is going to handle the evaluation doing, again, simple means on bleeding indices and gingival indices I don't think would cut it in this population. One would need a substantial number of subjects in the population because of the variance in their ability to develop plaque, in their variability in developing gingivitis, and then one would want to see how many of these -- who in the group, population group, changes, and by how much. So I think the simple use of indices and means would not be sufficient, I suspect, in a limited population of experimental gingivitis.

DR. BARNETT: And my colleagues can correct me if I'm wrong, but it seems to me there are qualifying entry criteria for these studies which specifies a certain minimum of plaque required in order to enter into the study. Again, I think we need to differentiate this from a trial that is specifically looking to demonstrate effectiveness, because that's already been done, as opposed to a method for a method for trying to assess whether a new formulation is in some way

comparable in effectiveness to your existing. And I guess the consensus, at least among us, is that the at least as good as structure is a way of getting around this, with getting the answer to this, within the short-term clinical trial.

CHAIRMAN GENCO: If we do suggest a human trial, is this the first for any OTC monograph? Dr. Soller, on page 13 in the recommendations, I don't know if this comes from you, your committee, or the FDA, but the statement is that these systems for monitoring do not create barriers to commerce, they define an efficient, predictable means to produce quality products at a reasonable cost.

I'd just like to ask Dr. Barnett, first of all, did I state that right, is that from NDMA?

DR. BARNETT: Yes.

CHAIRMAN GENCO: Okay. It's not from the FDA. The FDA has not made any statement about reasonable cost or barrier to commerce.

MR. HUTT: I will deal with some of the past history on that, but clearly FDA wants to reduce barriers, yes, and always has.

CHAIRMAN GENCO: Okay. Mike, what about the cost of a 125-patient, two-week experimental gingivitis study, is this in the realm of Stanley's green grocery now trying to market the fixed combination? Is this the kind of thing that's going to be a barrier to commerce? Stanley has quite a few stores.

DR. BARNETT: I think from the point of view of the manufacturer, given the size of the market, the cost of doing a two- to three-week experimental gingivitis-type trial would not be prohibitive.

CHAIRMAN GENCO: Further comments, questions? Bill?

DR. BOWEN: No.

MS. KATZ: Actually, I do have one comment. When the question was asked whether or not this would be the first testing proposed for humans, it is not. In the healthcare continuum, in a monograph there is proposed testing for humans.

CHAIRMAN GENCO: Thank you.

MS. KATZ: Actually, the other one, too.

DR. SOLLER: There is not in the final monograph.

CHAIRMAN GENCO: I think both answers are useful. There is a proposal, but there's none in the final monograph. Thank you.

DR. McEWEN: Dr. Gerry McEwen, I'm with the Cosmetic, Toiletry and Fragrance Association. There are two final monographs, one proposed and one final that have human testing. The tentative final that has human testing is the sunscreen monograph. The final monograph that has human testing is the antiperspirant monograph.

CHAIRMAN GENCO: So this is not groundbreaking -- I mean, if we need it, we need it, but --

MS. KATZ: That's correct.

CHAIRMAN GENCO: -- I just wanted to put it in perspective. Okay. Thank you.

DR. BARNETT: You dashed my hopes again, Bob, I thought I was going to be on the forefront of something new.

(Laughter.)

CHAIRMAN GENCO: Well, this is the first experiment for gingivitis. It was tried for the sunscreen, but it didn't work. Bill?

DR. BOWEN: Mike, I have a couple of details

particularly on the in vitro testing. I may have missed it, but I can't find any information on what was going to happen to the saliva samples, and if I missed it I apologize, but I can't find it.

And the second point, you make a very strong point concerning biofilms, and I'm wondering why the in vitro test is restricted to the planktonic state. Some of these microorganisms that you mention can be readily made into biofilms and make the in vitro test much more realistic.

The third point I have is that I know convention has it that serum be included, but in reality it's saliva that we're dealing with, and with due respect to the blood people in the audience, saliva "ain't" serum, and doesn't in any way resemble it, and I think we should start getting away from serum and getting to a more realistic test.

The other point I have is that I notice in your clinical study that you have 5 percent anhydrous alcohol as a control, but sterile distilled water as the control in the in vitro study. So, I wonder if you would care to comment.

DR. BARNETT: I forgot the first question. With respect to the in vitro and biofilms, I think the -- I mean, we're dealing with a real biofilm, a natural biofilm, in the clinical test. So I'm not sure how important it is, Bill, to also recapitulate that in vitro. I think the more critical aspect of the in vitro testing is to be sure that the spectrum of activity of the formulation, of the new formulation, has been retained.

With respect to how the saliva was handled, Dr. Penn may want to comment, but I believe that basically -- and perhaps it's hidden in here -- it's going to be handled in the same way as the -- Pauline, do you want to elaborate on that?

DR. PENN: Dr. Pauline Penn, Oral Care, Warner-Lambert Company. Dr. Bowen, with respect to your first question about how the saliva is handled, I believe it is in the protocol, that we recognize that there is variability in saliva and saliva microorganisms. The saliva we propose is a pooled sample of a minimum of six or eight persons. There are exclusion parameters for these people from whom we obtain the saliva. Under no

circumstances would the individuals be taking any prescriptions, antibiotics, or such antimicrobials. I hope this clarifies.

DR. BOWEN: I wasn't clear what you did after you pooled the saliva.

DR. PENN: The pooled saliva is tested the same way in the kill kinetics as all the pure cultures, namely, the salivary pool is added to your test mouthrinse at a fixed time, which is 30 seconds after incubation of the mouthrinse with the saliva microbes, and the sample is taken out and assessed and counted. So the endpoint measure is the same as the endpoint measure for the pure cultures.

DR. BARNETT: Bill, I'm sorry, I forgot the third point.

DR. BOWEN: The use of the 5 percent anhydrous alcohol as your control in the clinical --

DR. BARNETT: Oh, good. I thought that was the fourth, I'm sorry. Well, obviously, in the in vitro test, I'm told by my microbiologic colleagues that it is traditional to use sterile water as a control. You recall from the discussions we've had in the past about

what constitutes an appropriate negative control or placebo control in clinical trials, there was the feeling that it ought to at least have some resemblance to what could be an actual product in terms of color and taste and, therefore, that colored, flavored 5 percent anhydrous alcohol control has been used in clinical trials. And it's really so that people don't think -- don't know that they are using a negative control, which they would, obviously, if they were rinsing with plain water.

CHAIRMAN GENCO: Chris?

DR. WU: Well, I have a similar concern as Bill. If I could get back to the saliva samples. Do you know what is the starting bacterial count in the saliva sample, in the pooled saliva sample?

DR. BARNETT: I think Dr. Penn can better address that. I can't count that high.

(Laughter.)

DR. PENN: A routine salivary CFU per meal count for saliva is around 10^9.

DR. WU: Okay. Because it makes a difference depending upon the organism present, and the kill

kinetic data would differ. I have some more questions in regard to the protocol. If the serum is used -- I mean, the cells are first treated with serum and then treated with your test solution, what is the initial serum concentration that was used? Is it diluted, or just straight?

DR. BARNETT: Dr. Penn might as well stand up here.

DR. PENN: Dr. Wu, if you don't mind, I think I'll just stand here.

(Laughter.)

The way the protocol and assay is done is that an equal part of serum with the microorganisms are added, and then this, in turn, is, as per our protocol, added to the mouthrinse for the kill kinetics assay.

DR. WU: Depending on the organism, their susceptibility to the serum will be different, so if you treat them with serum, follow with the test organism, and you follow the same protocol, you would be left with different numbers of survivors, is that correct? So do you have a control just using serum and test organism minus the test solution, your mouthrinse -- do you have

a control for serum only?

DR. PENN: I think the answer is quite simple. We are trying to compare comparable activity of two different formulations, let's say, the control antiseptic mouthrinse formulation and presumably an experimental one. So, if we establish reasonable reproducibility in the in vitro test, then we can compare and see what a new or experimental mouthrinse would do.

There is no perfect methodology, Dr. Wu. I can critique and so can we all critique how and what ratio one adds, and also what kind of serum one adds, and so on and so forth. We would be here until eternity talking about this research. But we believe under the protocol that we've described and submitted to you, this is within microbiologic reason and a reasonable proposal, which gives us a standardized method to compare different formulations.

DR. WU: I have just a few more, just very minor questions. This technical concern, for example, you choose a battery of organism that you are testing, and I would assume that even one that's representative

of periodontitis or pyropathogens, or why wasn't P. gingivalis or P. inomenia chosen as opposed to F. nucleatum?

DR. BARNETT: The first three I mentioned, we selected because those are organisms which had appeared as recommended in previous or actually a final monograph for oral antiseptics. F. nucleatum was selected as a representative Gram-negative organism. As I mentioned earlier, there's no reason that another Gram-negative couldn't be substituted for that, or that the panel of organisms be expanded to include some periodontal pathogens. And certainly if you look at the range of organisms which are required, for example, by the ADA for their submissions, it is a fairly more extensive panel. So there is nothing to preclude expanding the panel, if that's what is believed should be done.

DR. WU: I think there is a mistake in your protocol under No. 7 kill kinetics assay, page 3. Is that one minute exposure but you were testing 30 seconds, so that might be a typo?

DR. PENN: Dr. Wu, the kill kinetics protocol methodology is meant for 30 second exposure. As you all

know, this under label usage for essential oil formulations, and that's what we proposed. If there is suddenly a one minute, I must have been on some other time factor flying back form Europe or something, which is --

CHAIRMAN GENCO: So that's a mistake, it should be 30 seconds on page 3.

DR. BARNETT: It should be 30 seconds.

CHAIRMAN GENCO: I'd like to follow up on those few questions and ask a general question. How specific are these standards usually? These are highly specific. In other words, four organisms, if the company doesn't use these four, does that mean they are in violation of not showing equivalence? I know there is specificity with respect to solubility and pH -- you know, those physical chemical characteristics, I understand that, but these are less -- these are biologic properties. I just wonder how much specificity we should have in selection of strains and that sort of thing.

DR. BARNETT: As I mentioned, three of those organisms actually have been very clearly specified in

a TFM in a very early 1982 work --

CHAIRMAN GENCO: Yes, but this is 1998, and strep mutans has nothing to do with gingivitis. Already it's out of date.

DR. BARNETT: Right, but your question is one of specificity, whether it's appropriate, and my only response is that it has been done in the past --

CHAIRMAN GENCO: I see.

DR. BARNETT: -- whereas the organisms -- you know, people might select different organisms. The specification of certain very specific strains, in fact, there's precedent for that.

CHAIRMAN GENCO: Maybe I could hear from the FDA with respect to that question, and then I have another one with respect to the statistics.

MS. LUMPKINS: My name is Debbie Lumpkins, I'm with the OTC Drug Division. By way of example, the healthcare antiseptic testing gives a very specific list of organisms. I would point out that this is just a proposal and that the list of organisms can change. But once that becomes finalized, manufacturers will be expected to have data on those specific organisms.

CHAIRMAN GENCO: That's my question. So, there is an option here. We could say a list of representative organisms of plaque associated with gingivitis and let the company decide, or be highly specific and say these four. So those are sort of extreme options that we --

MS. LUMPKINS: You have the option to make whatever recommendation you see fit.

CHAIRMAN GENCO: Thank you. With respect to the statistical analysis, the same sort of question then. You have -- the analysis here is based upon summary statistics means standard deviation, et cetera. And then you come up with a very specific .25 log, and I know what you're doing. It's like the statistically significant -- the bioequivalent is statistically significantly the same, they are not different statistically, but within a 20 percent variation. So your 20 percent analog -- there's a .25 log, and I just wonder where you got that and, you know, how are we going to deal with that.

It seems to me, given the variabilities of these microbiologic tests, that seems to be a very, very

stringent criteria, especially when you're looking at a 3-log difference, that's like a 10 percent. You're restricting the difference to -- if it's more than 10 percent, you've got something different.

DR. BARNETT: There is a precedent for that, Bob, and I'm going to ask Dr. Penn again to explain where that came from.

DR. PENN: I think I'm going to stay up here, Dr. Genco. It is not that tight a stringent requirement. In the official methods of analysis, the AOAC, specifically in the chapter titled Germicidal and the Sanitizing Effect of Disinfecting Agents, there is a specific reference that talked about -- that clearly states that agents must demonstrate comparable germicidal activity. And what is comparable? Comparable, in that particular chapter, refers to differences no more than .2, or we even were generous and made it .25, of a log difference from the standard.

CHAIRMAN GENCO: Are these agents that are just very, very active, either they just kill at 10 log, 7 log difference?

DR. PENN: These are agents that are quite

active.

CHAIRMAN GENCO: That's my point.

DR. PENN: These agents we believe are valid to compare for the following reasons. First, it's topically applied. Secondly, these agents are exposed for a short duration. The same is true for oral rinse conditions, 30 seconds, topically applied, no abrasions. So, therefore, we believe there is validity in asking for such stringent requirements.

And, finally, thus, has been publicized and is well known. The standardized essential oil mouthrinse, as we know today, is quite potent and can easily reduce by many logs. So the likelihood of a comparable agent being the same, if it is as effective, it will meet this stringent requirement.

I think the objective is to throw out the real dogs of the formulation and to make things easier for all those concerned.

CHAIRMAN GENCO: Thank you. Ralph, did you want to comment?

DR. D'AGOSTINO: Yes. I don't know how the panel is looking at the protocol, but I wouldn't -- from

the statistics, I wouldn't take it as rigorous, must be from now on, but more as guidelines. I think the steps that are suggested and the sort of statistical analysis procedures are reasonable, but I hope we don't end up making a recommendation that this is the only way to do it. I mean, you want some flexibility. I never bought into this at least as likely or as good as and all that, and I think a number of other statisticians -- and certainly there's no reason for us to tell the FDA that they should buy into that vocabulary. I think it's a reasonable number of steps, but I hope we give a blessing of anything as a guidelines, and the same for the questions that you're raising, that those issues have to be faced but the particular numbers aren't necessarily the right numbers and ones that we should really buy into.

CHAIRMAN GENCO: So you would opt to language that the formulation was substantially equivalent as assessed by reasonable statistical analysis.

DR. D'AGOSTINO: And, you know, for example, look at what's here, but this is -- you know --

CHAIRMAN GENCO: For example. Right. Okay.

Max, and then Bill.

DR. LISTGARTEN: Two comments. I want again, with respect to the statistics, I think it may be much more difficult to show equivalence than it may be to show superiority of one product to another. And I think in terms of size of the study to show equivalents, you may run into a real problem. The numbers may become extravagantly high, that's to prevent a Class II error.

The other question I had had to do with the human trial. Is one trial enough?

CHAIRMAN GENCO: Do you want to answer that?

DR. BARNETT: I don't know. I guess the question --

DR. LISTGARTEN: We don't usually buy one trial.

DR. BARNETT: Yes, I know. I mean, I would agree with you, but again this is a recommendation for the type of trial. I really think it's up to the panel to decide whether one is enough, two is enough, three is enough. On a personal level, Max, I share the same concerns in interpreting one that you do, but I really think that's a question of what seemed appropriate for

that specific purpose, and I really think it's this subcommittee that needs to make that determination.

DR. LISTGARTEN: I guess my big concern is to show equivalence you need a very large study, and then you're going to need someone to -- you're going to need at least two independent studies to make any kind of sense. And I'm sort of worried that this is getting to be a very big enterprise for something that's supposed to be quick.

DR. BARNETT: Max, I think, though, that in terms of the recommendation was not a study that showed equivalence because it was recognized that, in fact, that would be a very unwieldy study, and perhaps prohibitive as well. So the proposal then was to -- excuse me, Ralph -- but this at least as good as type of structure which is not quite as extensive as the study that would be required to show equivalence certainly in terms of numbers of subjects. That was the intent of proposing that as opposed to a study demonstrating equivalence of two formulations.

Again, I think going back to Bill Soller's presentation talking about reasonable expectation, I

think we need to keep in mind what we're trying to accomplish with these various performance tests.

DR. D'AGOSTINO: They also build in the protocol that they're not really saying equivalence, they're saying within 10 percent, and that's where this at least gets, and it takes you somewhat from the concerns that you have, that it's not going to be A equals B, but A differs from B by no more than 10 percent. And the question I'm raising is, do you want it as an interval or do you want it only on one side of the confidence interval. I think the notion of 10 percent or something like that makes sense for equivalence or for sort of clinical equivalence. Whether it should be one-sided or two-sided, I think that's something that the manufacturer could put forth and argue or discuss with the FDA, and that's the thing I don't think we need to give a hard and fast blessing on. But I agree with you that equivalence would be very high.

One of the things that keeps happening in these type of discussions that always is hard to avoid is that we talk more and more about them, and the more

we talk the more we get back to basically running our original clinicals, and this is somehow rather in between. You have a formulation and you just want to make some changes, and what do you do at that point. And I think the protocol -- I think the protocol -- from a statistics point of view, has a lot of good merit to it, and I think from a clinical, if I hear, it makes a lot of sense also.

CHAIRMAN GENCO: Bill, and then Lew, and then Stan.

DR. BOWEN: I think it's important that we don't lose sight of the fact that we are looking at formulations that essentially should have the same ingredients as the originally tested product. And, therefore, the stringency of testing should not match or even come close to that of the original clinical trial.

I want to get back to the question of the specific organisms and, as Pauline indicated, this is a dilemma that we will discuss ad nauseam. The use of American type culture collection strains is always fraught with difficulty because after these have been subcultured a few times in the laboratory, they no

longer resemble, in many respects, the original life of it. And, indeed, there's clear evidence that many of them will change over time. So, undoubtedly, we generate from organisms isolated 15 years ago may not in any way resemble that of what had been collected many years prior to that.

I doubt that you have any problem in meeting the 0.25 log difference with the pure cultures. I am a little concerned that you may have loaded against yourself with the saliva because when you are dealing with salivary organisms, as you know, you have a big problem with dispersion, and then your standard deviations and standard errors creep up enormously, so you could have a problem there -- a technical problem.

CHAIRMAN GENCO: Thank you. Lew.

MR. CANCRO: I think this discussion must be kept in perspective, that it is concerning a single submission of fixed ingredients, and that what the manufacturer is attempting to convey is that you have already determined these ingredients or this fixed combination to be clinically effective. You did that. You've already done that. And the manufacturer is now

proposing for this fixed combination, in effect, a profile of tests by which you can be more than assured that nothing has happened to this fixed combination as its formulation may change, or as its manufacturing processes may change.

And the answer to the question is, one, is one model clinical trial sufficient, from my perspective, it's more than sufficient because the formulation is already matching a great number of physical tests, microbiological tests, whatever they are going to be, and additionally a clinical model test.

So, to go back to the premise, you're not reinventing the wheel here to determine that the ingredients are active all over again and let's get started again, you simply have to use reasonable judgment that the profile of tests recommended by the manufacturer matches the standard.

CHAIRMAN GENCO: Stan?

DR. SAXE: Yes. Another cautionary note, first of all, let me say that I think it would be great if we could get a small number of human beings in the clinical component and do the testing with the least

number and a small number.

Let me say that there might indeed be a need for a second batch of 105, and why it might be. I would hope not. I would hope that one simple study would do it. All of the subjects meet, as you pointed out, the certain minimum score on plaque and certain minimum score on gingivitis. In the protocol you listed it was 1.95.

Several individuals, a number of individuals, may score around that or have a minimum of 1.95. If they are stopped from practicing self-care, they will not all look alike after a week or after two weeks. Some of them have as low a score as, let's say, a 1.95 because they are practicing good self-care. If they weren't, their scores when they show up at baseline would be much higher. So some of those who have been doing good in self-care, once they are prohibited from self-care, from brushing, whatever means they are using for oral cleaning, however they would describe it, will take off and may have a lot of gingivitis in a couple of weeks, may have a lot of plaque.

Roughly maybe 5 to 10 percent of the

individuals will be like this. If, with 105 in the total population, you've got a group of 35 in the original four essential oil group, and then there's a new formulation, it may well be that when you interfere with the standard with the four essential oils, you really cut down on those high gingivitis scorers. Six of them might end up in that group and one might be in the new formulation group, and it would look as if the new formulation -- because they will weight their population so heavily -- it will look as if that the high scorers, the high gingivitis folk, if they mostly end up in one of the groups, that the second formulation, the second group, will differ and not do as well.

I'm saying that if you've only got 70 people and seven of them -- okay -- there's no guarantee in one study that they are all going to fall -- you know, if you've only got a group of 35, that they are going to have three in one group and four in another.

DR. BARNETT: I guess what I'm confused, Stan, I'm not sure on what basis -- on what evidence we're suggesting that a small subpopulation is going to be --

DR. SAXE: Years ago, when it wasn't difficult to get people to brush, we could do 50 dental students at a time to simply stop brushing for a week. You can't do that for many, many years now, and you could see that in a group of 50, you could get five or six that would just go off the scale in terms of once plaque control was stopped. And it's kind of consistent, or had been consistent in that way. So, I'm just saying with a small population group of 35 individuals in one group and 35 in another and you're drawing these from the same pool of 105 individuals, there's no guarantee with such small numbers that they are all going to fall -- be equally distributed among the three groups. It's a cautionary note. It would be great if they were, but I'm saying if things don't work out in the first trial, it may well be because of the distribution of subjects.

DR. BARNETT: You've answered Max's question then.

DR. SAXE: That you might need a second one to confirm it.

CHAIRMAN GENCO: Let me make a comment --

DR. LISTGARTEN: I just wanted to comment on -

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CHAIRMAN GENCO: Let me just make a comment about this issue. It seems that the air here of concern is that the new age, that the new formulation test positive in the two-week clinical trial, but doesn't work. So it's on the market, doesn't work. Now how often does that happen? I think what you presented is the opposite, that if it doesn't work in the trial then the company would probably do a second trial anyway. So what we want to protect against is the false-positive which -- for a negative agent.

Now, Mike, in your experience, how often would that happen? I mean, you must have tested many formulations. Did you ever get one that didn't work in the two-week gingivitis and worked in the six-month, or worked in the two-week that didn't work in the six-month?

DR. BARNETT: None that I can recall in our experience, Bob.

CHAIRMAN GENCO: So I think that's the answer.

DR. LISTGARTEN: I just wanted to comment on -- I think you misunderstood how these patients are

screened for these clinical studies. I think they are asked to stop oral hygiene to see how fast they form plaque and gingivitis, and then they are selected on that basis. These are not selected while they are going on doing their regular oral hygiene, so I think some of your concerns are not --

CHAIRMAN GENCO: Sure.

DR. LISTGARTEN: Isn't that the way --

DR. BARNETT: Yeah, there's a period of time, I'm not sure how long it is, but there is --

DR. LISTGARTEN: There's a preclinical trial testing going on during which you select patients who do not brush their teeth, and you only pick those who, in fact, do get gingivitis and do form plaque. So, it's a little bit more homogeneous than what you suggested, so I'm not as concerned about that.

CHAIRMAN GENCO: Let me make a suggestion about the rest of the afternoon. It's clear that we're going to have to take each agent separately. We have a discussion of stannous fluoride CPC which is triggered by Dr. Bowen's questions to P&G and P&G's response. We also have another issue with respect to the fixed

combination, and that is if it were used in another form, dosage form like a toothpaste.

What I'd like to suggest while all these issues are in mind, that we now go to the questions for the mouthrinse fixed combination. The first question is, is final formulation needed? Second question, are there surrogate tests, et cetera? And I think we can maybe discuss that, unless Warner-Lambert would like to have their presentation on the other dosage form first.

MR. HUTT: I think the next presentation is actually related to this and it comes as a unit, really, so I think we prefer to do that.

CHAIRMAN GENCO: Okay, fine. Approximately how much time would this take? Peter?

MR. HUTT: I would say a total of a half-hour, 15 and 15, roughly.

CHAIRMAN GENCO: Okay. It's 2:20 -- why don't we do this. Why don't we take a ten-minute break now and then start at 2:30 for that presentation.

(Whereupon, a short recess was taken.)

CHAIRMAN GENCO: We have two presentations from Warner-Lambert, the first by Peter Hutt, and then

Bruce Kohut. Peter.

MR. HUTT: Thank you, Mr. Chairman. For the record, I am Peter Hutt. I am appearing today on behalf of Warner-Lambert to discuss one very specific and narrow aspect of the monograph system, and that relates to the handling of dosage forms in the OTC drug monographs in general, and obviously in the plaque and gingivitis monograph in particular.

I think it would be useful, Dr. Genco, for me to explain how these three presentations for me to explain how these three presentations for Warner-Lambert fit together. What we have just heard is Michael Barnett describe for one specific dosage form, namely, the mouthrinse dosage form, the likely or recommended method of performance testing to assure that all future formulations using the four essential oils would all be effective.

What I am going to discuss is the overall regulatory approach that prior panels and the FDA have always taken in these monographs, not for specific dosage forms but to permit all reasonable dosage forms. In short, what I will recommend to this panel is that

there be no limitation on dosage forms, but that any dosage form that is -- and I will give you a quote -- "suitable for topical administration to the teeth" ought to be permitted under the monograph subject, of course, to reasonable limitations and restrictions of the type that Michael has already described for the one dosage form, namely, the mouthrinse.

And I will be followed by a third presentation by Bruce Kohut, who is going to discuss the scientific and technical issues that one must address when you expand from the one dosage form that has been uniformly tested, the mouthrinse, to include all of these other reasonable dosage forms that typically are permitted under the monograph system. Those considerations would include consideration of dosage level and of additional types of performance testing to assure that the other dosage forms would also be of comparable effectiveness.

I will divide my remarks which relate to the regulatory side before Bruce discusses the technical and scientific side, I will divide my remarks into two parts: one, I want to address some of the broader questions that many of you on the subcommittee have

raised about, if you will, the philosophy, the way that FDA has in the past gone about this, and then, second, I will deal specifically with precedent in the form of particular tentative final and final monographs that incorporate these general concepts.

Let me go back in terms of the historical overview to some of the things that were covered by Bill Soller, but I will instead -- Bill tried to deal broadly with the monograph system, I want to focus specifically on this unique issue of how to handle dosage forms under the monographs.

Now, let me repeat a little bit of what Bill said, the dilemma that FDA faced in 1971. That dilemma was a very serious one because, as Bill pointed out, it was impossible to handle 150,000 products using new drug applications, but it was more than just that.

There was a prevailing philosophy in FDA that the widest possible variation of over-the-counter drugs should be permitted under the OTC drug monograph system as long as there could be assurance of safety and effectiveness.

Now, to be sure, there had to be assurance of

safety and effectiveness, but the philosophy was chosen from the first day, and it has prevailed to this day, that restrictions should only be imposed where they are necessary -- and I use that word in the literal sense -- necessary to assure safety and effectiveness. In short, there should be no limitations through the monograph system simply for the sake of limitations, they should be there for a very specific safety and effectiveness reason. Otherwise, from the beginning, it was thought that the broadest possible scope should be given to the monographs in order to permit creativity, in order to permit as unrestricted open marketplace in over-the-counter drugs as is consistent with safety and effectiveness.

Now, this was handled, of course, by using a monograph rather than an NDA system, and by posing to each panel over the years -- and it's now 27 years of panel meetings, I'm amazed to say -- wherever any issue arose, the issue was always, how can we assure safety and effectiveness of the product with the least necessary restrictions? And in terms of dosage form, the way it was handled was the presumption that all

reasonable available dosage forms should be permitted under the monographs, subject only to the possibility if someone could identify a dosage form that was unsafe for some reason, some specific reason, or would be ineffective for some specific reason, then that of course would not be permitted.

Absent some kind of a finding of that -- and we will see this in very specific terms as we go through some of the monographs in just a moment -- absent a finding of lack of safety or lack of effectiveness, the monographs have uniformly permitted all reasonable dosage forms.

Now, Dr. Genco, you raised this question as to how you make those kinds of determinations. You raised questions of the FDA representatives, and Ms. Lumpkins gave the answer that has been given for 27 years, it is the judgment of the panel as to whether a restriction is necessary. There is no rigid rule that can govern that scientific expert judgment that the people who sit around this table bring. And that has, I think, been the touchstone from the beginning.

Now, let me describe for you in a sense a

broad construct of how every panel has gone about this. There have been three determinations that have been essential for every panel deliberations in looking at individual active ingredients. The first question, the first determination, is whether a specific individual active ingredient is safe and effective in at least one tested dosage form. I am unaware of any active ingredient that has ever been tested in every conceivable dosage form, but the first determination is, is the ingredient inherently safe and effective? Can it be formulated in a way that it will provide to the consuming public the benefit for which it is claimed? That's the first determination.

Then one looks as a second determination, is there any reason to limit it to certain categories of dosage forms? The presumption has always been any form of dosage, any kind of carrier, any way of formulating the product ought to be permitted, as I said, unless there is a reason to restrict it. Thus, that second determination is, is there some unique safety or effectiveness reason so that all -- all -- available dosage forms should not be permitted?

And then the third determination is along the line that Bill Soller described. In order to make certain that all these other dosage forms will be of comparable effectiveness, what, if any, restrictions should be -- or limitations or requirements -- should be imposed?

Now, some of those requirements and restrictions and limitations are easy. In some instances, for example, either a specific concentration or a range of concentration for an active ingredient is specified. As I will illustrate in one moment, though, even that is not uniform. There is at least one monograph that has no range or point limitation for the amount of the active ingredients to be included in the final formulation.

A second area is, of course, to set chemical specifications, and that is -- at the beginning, it was often done in the monographs themselves. Some of those kinds of requirements have now, in effect, been shifted to USP.

And then the third area is the area of performance testing and, again, Michael Barnett has just

finished a lengthy discussion -- and you have asked him many questions -- about the kind of performance testing that would be appropriate for one -- but I emphasize "only one" -- dosage form. One must look at that same issue for all other appropriate dosage forms for the same active ingredient, i.e., the fixed combination of essential oils and also for the other Category I active ingredients that are involved as well.

Now, with those general comments, let me turn very specifically to the submission that Warner-Lambert made to Bob Sherman on May 13 of this year. I'm sure you all have it in front of you. I simply want to bring to your attention that Part I of this lists dozens and dozens of OTC drug monographs, and lays out how panels and FDA have dealt with this issue of dosage forms in those specific contexts of individual monographs. And I am going to summarize this. I will do it as quickly as I can, but this is such an important issue in light of the prior discussion with Dr. Barnett that I want to make sure everyone on the panel understands it.

The first category of monographs -- and these are final monographs, and it's right on the first page

of Part 1 of this submission -- is monographs where the OTC active ingredients are approved -- and this is a direct quote -- "in a form suitable for oral administration". In short, with no limitation upon the type of dosage form other than that the drug would be taken orally. And you will see on the next page there is a long list also of OTC drugs approved in -- and, again, a quote -- "a form suitable for topical administration".

Now, in both of those instances, it is left to the scientific creativity and ingenuity and technical ability of the manufacturers to think up new dosage forms, new ways of serving the consumer, new ways of presenting a safe and effective active ingredient in a dosage form that will perhaps do a better job for the consumer, be more convenient, be more acceptable, be cheaper, or whatever. That has not been a limitation imposed on FDA other than for safety and effectiveness reasons.

And let me put your eyes right to what FDA and the panels themselves have said about this. If you look at the second page of Part II, there is a quotation from

a preamble that FDA put in the Federal Register where the following statement is made -- and I will read it in case all of you do not have it in front of you. "The panel did not intend to restrict ingenuity and product design as long as the product accomplishes the claimed effect and met the same final formulation requirements of safety and effectiveness as any other dosage form. Other final monographs are similarly expansive in their permitted range of dosage forms." This quote, if anything, best captures the philosophy both of the panels and of FDA.

Now, I could go through dozens of these but, Dr. Genco, I know you are anxious to get on with discussion, and I'm just going to therefore turn to two other quotations from FDA that illustrate how the Agency has handled this in the past.

If you look a couple of pages on, you will see a Footnote 26. This was a situation where in the analgesic monograph, FDA was asked by industry, please specify a particular dosage form. And FDA's response was, "No, we won't. We don't need to because we intend to permit any appropriate oral dosage form". That's a

summary of that quote.

More recently, just in 1994, this issue arose in the context of topical anti-infective products. The industry asked FDA to specify in the monograph a particular dosage form, namely, antibacterial soap. And once again FDA said, "No, we don't need to do that. That is merely another dosage form of anti-infective, antibacterial, antimicrobial products, and there is no reason to specify the dosage form because our job in FDA, and the panel's job, and the monograph's job, is to set forth the general criteria that will assure safety and effectiveness of these products in any dosage form, all dosage forms".

So, in conclusion, what I'd like to suggest is that I again remind you of that three-step process that every panel goes through. The first step, as I mentioned, is to make certain that the active ingredient -- and this includes all the Category I active ingredients, not just the fixed combination of essential oils -- but to make certain the active ingredient in at least one well tested dosage form has been shown to be safe and effective. And for the Category I active

ingredients, I don't think there is any question about that.

Then the second determination has to be made, is there a safety reason why that active ingredient could not appear in another dosage form, or an effectiveness reason? And I would suggest that thus far in listening to a discussion of the various Category I active ingredients, I certainly have not heard of a safety or effectiveness reason why that could not be done.

Then we get to the heart of the issue and what Bruce Kohut is going to be discussing. Assuming those two determinations, the task ahead is to determine what performance, what specifications, what dosage levels, what other restrictions are necessary in order to assure that all these other dosage forms of the product containing the same active ingredient will have comparable -- to use the word that's been used -- comparable degree of effectiveness, so that the consuming public will have available a wide variety of products, the marketplace will be a free and open marketplace consistent with our American tradition, and

yet we make certain, which we must make certain, that the finished dosage form, whatever it is, is safe and effective.

Mr. Chairman, I'll be happy to answer questions, or if you would like to defer them until after Dr. Kohut, I'll do it either way you wish.

CHAIRMAN GENCO: I think maybe we could entertain questions or comments now. Yes, Bill?

DR. BOWEN: You dealt with events on dosage form, but -- if I missed it -- I didn't hear you deal with the issue of higher concentrations in different dosage forms, which is a slightly different question.

MR. HUTT: What you are raising, Bill, is the question of a potential range of levels of permitted ingredients in a single type of dosage form. Let me just reiterate, there are two ways of handling that. The panel, in its expert judgment, can either determine that you should set a fixed level or fixed concentration, or you can determine based on the evidence presented to you that a range of permitted concentration is perfectly permissible. That's a matter of scientific determination, and I will tell you, I

could show you monographs that go both ways on that. Some panels have determined for a particular ingredient, well, 2mg is the dose. Others have said a concentration between 1 and 2 percent is acceptable, but that isn't a regulatory issue, that is a scientific judgment issue for all of you on the subcommittee.

And Dr. Kohut will discuss very specifically that issue in the context of dosage forms other than a mouthrinse for the fixed combination of essential oils.

CHAIRMAN GENCO: Peter, I'd like to ask, in the spirit of what's been done before, there's probably ten or twelve possibilities of applying the fixed combination, certainly the oral rinse -- that's where the data is -- toothpaste could be applied in a gel which could be put in a mouthpiece, or a gel applied to the gingiva, could be put in a gum, could be put in a lozenge, could be put on floss, could be put on a toothbrush, could be put on a slow-release pellet attached to the tooth. Are we -- is it usual to deal with all of those individually, or how do we be inclusive of all that we know about and think about today, and there may be ten more that we can't think

about.

MR. HUTT: Well, to begin with, the usual way of handling it in the monograph is to use the type of broad language that I've quoted here, a form suitable for oral administration, a form suitable for topical administration, or the one that I gave you right at the beginning which happens to be the one out of the anticaries monograph, in a form suitable for topical administration to the teeth. That's the way it is put in the monograph on anticaries drugs. But the more important question is, do you have to think of all these?

Let me add just one -- you may find it humorous -- why couldn't you do it in a spray, you know, a little spritzer? There are lots of different ways that if we sat here for six weeks we would not think up all of them. The point is that if this kind of language is used in the monograph, what your job is is to find a way -- and I believe it can be done -- to permit a broad enough form of product testing and product specifications so that no matter what it is that we're talking about in terms of dosage form, it will be safe

and effective when it's used in the oral cavity. That's the job.

CHAIRMAN GENCO: It seems to me that there is a very unique problem, possibly, and that is formulation inactivating, I mean, that's the rule rather than the exception.

MR. HUTT: That is correct.

CHAIRMAN GENCO: So I think we'll have to be obviously concerned with that. Any of these formulations could easily inactivate.

MR. HUTT: And, therefore, without any question in my mind -- and Bruce will deal with this very directly -- you clearly need a performance test, without any question whatever. It would be irresponsible for any manufacturer to put out one of these merely on the basis of chemical specifications because you would have no certainty it had reached the tooth.

CHAIRMAN GENCO: I guess we could craft a performance and give as example the one that Warner-Lambert suggested, the two-week gingivitis, but that may not cover all the possibilities for release. In other

words, how is this generally done? In other words, there may be a performance that, again, we haven't even thought of, that would be relevant to testing a particular formulation or dosage.

MR. HUTT: Well, I have some reason to believe that the gentleman who follows me will have an answer to that question, and will, indeed, propose a form of performance testing that -- at least according to my logic, Bob -- would apply no matter what the dosage form was.

CHAIRMAN GENCO: Any other questions of Peter while he is at the podium?

(No response.)

If not, thank you very much.

MR. HUTT: Thank you.

CHAIRMAN GENCO: Let's proceed then to Bruce Kohut.

DR. KOHUT: Good afternoon. For the record, my name is Bruce Kohut. I am Director of Oral Care Research, in the Worldwide Consumer Healthcare Research and Development Division of the Warner-Lambert Company. I appreciate the opportunity to speak to you this

afternoon on the subject of oral dose forms for Category I antiplaque/antigingivitis ingredients.

Mr. Hutt presented the regulatory basis for the delivery of antiplaque/antigingivitis ingredients. I would now like to present a scientific rationale for establishing permissible levels of an active ingredient in different dosage forms and the performance tests required to assure the effectiveness of the final formulation. While my comments focus on an essential oil dentifrice, they are, I believe, in principle, applicable to both other oral dosage forms and other Category I active ingredients.

Different dosage forms will most likely require different concentrations of an active ingredient. A dentifrice, for example, would always have a higher concentration of an active ingredient than a mouthrinse in order to deliver comparable levels of the active because a lower volume of dentifrice is used.

This table displays a summary from published studies on mouthrinses and dentifrices containing representative active ingredients. It shows the concentration in these dose forms and the ratios of

dentifrice to mouthrinse concentrations. Triclosan was shown to be an effective antiplaque/antigingivitis agent in a dentifrice at 10 times the concentration in a mouthrinse, 0.3 percent vs. 0.03 percent, and chlorhexidine in a dentifrice at 8.3 times the concentration in a mouthrinse.

The concentration of an active ingredient in any appropriate oral dose form is determined by safety and effectiveness considerations. Safety can be assured by specifying an upper limit. However, when establishing this upper limit for different dosage forms, it is easier to consider the milligram amounts of the active to be delivered per dose rather than the concentration in the final product.

For example, this table displays the milligram amounts of the four essential oils as a fixed combination as well as the total amount of the fixed combination in a 30 ml dose of the essential oil mouthrinse. For example, Thymol at 12.8 mg, Eucalyptol at 18.4, Menthol at 8.5, methyl salicylate at 12.0, for a total of 51.7 mg. The same values are presented for a 2 g dose of a dentifrice containing the essential oil

fixed combination at 10 times the concentration in a mouthrinse. The total delivered amount of the fixed combination is the same in both cases, 51.7 mg.

Since safety has already been established, the upper level for the essential oil fixed combination in any oral dose form should be based on the milligram amounts in a mouthrinse dose. A dentifrice, could therefore be formulated for safety considerations at no greater than 10 times the concentration in the mouthrinse.

The lower permissible level, on the other hand, should be dictated by effectiveness as demonstrated by clinical testing. The milligram amounts of the active ingredient delivered may not necessarily have to be identical to those derived from other dosage forms since there are differences in intraoral use conditions. In the case of a dentifrice vs. a mouthrinse, access to the plaque biofilm is much different. In toothbrushing this biofilm is disturbed, while in rinsing the mouthrinse has to penetrate the plaque biofilm. Amounts of an active ingredient less than those delivered in a mouthrinse may be effective in

a dentifrice.

As part of our dentifrice dose ranging program, we conducted a short-term three-week plaque and gingivitis study evaluating a dentifrice formulated not at 10 times the mouthrinse concentration as I just discussed under safety consideration, but at 8 times the fixed combination concentration in the mouthrinse. A 2 gram dose would therefore deliver 80 percent of the mouthrinse dose. The results of this study were presented at the American Association for Dental Research Annual Session this past March.

The abstract shown here was included in our submission to you. The tested dentifrice significantly reduced plaque and gingivitis under the condition of the study. The results of this study suggest that a different dose form delivering approximately 80 percent of the mouthrinse dose can be an effective antiplaque/antigingivitis dose. Thus, the results of this study help support the premise that when formulated in a different dosage form, an identical milligram amount of active ingredient does not have to be delivered in order to be effective. A concentration can

be permitted that delivers less than the milligram among of the active present in the original product form.

It is imperative that performance test be required to assure the effectiveness of the final formulation of these different dose forms. Although the preference for monograph performance testing would be short and less extensive tests such tests cannot be reliably used to demonstrate the effectiveness of a Category I active ingredient in a different dose form until both the short-term model and the appropriate reference standard are validated. Where no such model or validated reference standard exist, effectiveness should be demonstrated by performance testing consisting of a six-month clinical trial conducted and evaluated according to the standards utilized by this subcommittee in reviewing Category I ingredients. At such time as a reference standard is established and less extensive performance tests are validated, FDA may amend this requirement either administratively or through the petition process.

In conclusion, it is our position that a permissible range of levels for each Category I

ingredient should be established for use in any oral dosage form suitable for topical administration to the teeth. The upper level should be based on safety as determined by the delivered milligram dose for the originally accepted dose form. As an example, in the case of the essential oil fixed combination, the permitted level for all dosage forms should result in the delivery of no more than 51.7 mg. For a dentifrice, this would be 10 times the concentration of the mouthrinse.

To establish a lower limit, effectiveness should be considered. You have already determined the effectiveness and safety level for the essential oil mouthrinse. For the other oral dose forms which require a higher concentration, such as a dentifrice, a lower limit of at least 8 times the concentration of the mouthrinse is consistent with existing published studies on other actives and our dentifrice data to date. A permissible range for a essential oil dentifrice would therefore be 8 to 10 times that of the mouthrinse.

Effectiveness in the essential oil dentifrice or any new dose form must be demonstrated through

performance testing. If no validated study design or reference standard has been established, effectiveness through performance testing should consist of a six-month clinical trial satisfying standards utilized by this subcommittee.

Warner-Lambert respectfully requests that this subcommittee affirm that Category I antiplaque/antigingivitis ingredients may be formulated in any oral dose form suitable for topical administration to the teeth under the conditions of the specified range of the active ingredient and designated performance testings.

I thank you for your attention. I or one of my colleagues will be happy to respond to your questions.

CHAIRMAN GENCO: Thank you, Bruce. Any comments, questions? I'd like to ask why you would like to require a six-month clinical trial, let's say, for a dentifrice containing the fixed combination when you already showed the three-week trial showed efficacy, which is not too different than a two-week experimental gingivitis. I guess what I'm getting at is if the two

three-week gingivitis model is reasonable for the oral rinse, and it looks like from your one trial here with the dentifrice, couldn't that be a performance standard for the spritz or the spray, for a gel, for incorporation in floss, whatever?

DR. KOHUT: There are two important distinctions. One is that the three-week model is not yet validated. We have not yet shown the validity of that model in relationship to six-month testing. The other aspect of it and the other shorter-term models that we have suggested, there is a clinical standard that's in that model, and so it helps put into perspective what the results are of that short-term model.

CHAIRMAN GENCO: Clinical standard, you mean the positive control?

DR. KOHUT: Yes.

CHAIRMAN GENCO: Further comments, questions? Bill?

DR. BOWEN: The problem with the three-week model, of course, is that oral hygiene is suspended anyway, isn't it?

CHAIRMAN GENCO: It's like the experimental gingivitis two-week, really.

DR. KOHUT: I'm sorry, the three-week model is a brushing model.

DR. BOWEN: the question I have for you, Bruce, is, are you concerned at all by the fact it's a different formulation -- for example, a toothpaste and a gel usually result in much more of the product being swallowed than if they are in a mouthrinse form, and we are seeing perhaps in some parts of the world the consequences of this with the fluoride toothpaste.

DR. KOHUT: We think that a sufficient safety margin exists with the 51.7 mg that that should not be an issue.

CHAIRMAN GENCO: Further comments, questions?

(No response.)

So to summarize, we're left with this dilemma that's presented to us by Peter and Bruce, one is not to put barriers too high for innovation, and Bruce says, well, we've got to put a very high barrier, that you've got to start from scratch for all these new formulations. What does the panel think of that? I

mean, essentially, that's what you're saying.

DR. KOHUT: That's correct.

MR. HUTT: Could I just add one qualification because if the panel were only to be very limited in the permitted dosage form, the alternative would be a full new drug application, and thus the requirement of a six-month study is substantially less than it would be otherwise, Bob. Do I make myself clear on that?

CHAIRMAN GENCO: Yes. But it's still a significant financial barrier.

MR. HUTT: Yes, it is, but it's an attempt to find as low a barrier as is reasonable from a scientific standpoint to assure safety and effectiveness and, as Bruce pointed out, shorter-term, less expensive, validated standards could be found, they could be substituted for the six-month.

CHAIRMAN GENCO: Two reasons for the three-week brushing study not being validated is, number one, the dentifrice hasn't been tested for six months and compared to the three-week result.

MR. HUTT: That's correct.

CHAIRMAN GENCO: The second is that the three-

week result doesn't have a positive control. That's easily solved, just add a positive control, so that one doesn't count. It's the first one, the validation vs. dentifrice, or whatever formulation, for six months, assuming that's the gold standard.

MR. HUTT: That's correct.

CHAIRMAN GENCO: Okay.

DR. McGUIRE-RIGGS: I'd like to make a couple of points of clarification. In terms of the monograph, since we could have quite a range of dosage, but back to Bill's point about concentration, we need to be very specific on what we feel is the range of concentration that is both safe and effective, since that is what it kind of all bases itself upon. And, secondly, how -- does everybody agree that a dentifrice is 8-10 times the mouthrinse concentration, is that a generally held and acceptable premise?

MR. CANCRO: I think that's going to vary on the nature of the active. The issue here is the principle. Ingredients have been shown to be active in both a liquid and a solid form, albeit at this point they are different ingredients. What is being proposed

is that at a safe concentration, the active ingredient can be placed in another form and delivered in exactly the same effective amount via a different way of doing it, with no elevated safety concerns. Now, that takes into account when you are formulating from a liquid to the solid form, the nature of the ingredient making the change. And that will limit your use of various excipient ingredients, depending on what your active is.

In this situation, the manufacturer has presented you with a pilot study showing you that in two weeks the ingredients are being delivered. The indications are being upheld. And, further, they are even proclaiming that the validation of that proof of principle test is the six-month trial. But the important consideration is, can you change dosage forms under some guidelines, be it 8 times, 10 times, or in some other cases whatever the ingredients are, 12 times, 6 times, et cetera. I think it's the principle, which has already been accepted as an OTC principle, that obviously forms can change. It's a case of delivering it.

So, when you look at different ingredients,

they may be restricted in terms of what you can formulate with, but is it possible to do it? I think this manufacturer has shown in this situation it is possible.

CHAIRMAN GENCO: Bill?

DR. BOWEN: It isn't simply a question of dosage form, it also is a question of concentration because if you take a mouthrinse with .5 percent in it, it may not cause any problems whatsoever either in staining or disclamation. On the other hand, you can then increase it by 10 times and now you are applying a 5 percent solution -- admittedly, the total exposure is the same -- and you may end up with much more intensive staining and, indeed, disclamation with the same dosage form because the concentration differs.

MR. CANCRO: That's entirely correct, Bill, and with the application of the longer-term clinical, obviously, that's got to be looked for. I mean, local effect, staining, that's all part of the longer-term clinical. Maybe it was part of the shorter-term clinical, I don't know, but they are very valid questions which would presumably be answered in the

pivotal study.

CHAIRMAN GENCO: Sheila.

DR. McGUIRE-RIGGS: I just worry that there could be a blurring of the line between over-the-counter and prescription at some of these interactions of dosages and concentration. When do you make that leap to it being a prescription formula?

MR. HUTT: If I could comment on that, I don't believe there would be a blurring of the line because, as Bruce pointed out, you would set the upper level at the maximum that was tested in the case of the fixed combination of essential oils, that would be 51.7 mg delivered dose, so that there would be a clear delineation in those areas where there is a higher prescription level between the OTC level and any higher prescription level.

DR. McGUIRE-RIGGS: I just think we should think through that.

MR. HUTT: Yes, I agree with that. And it may be that if that would be something that would be ingredient-specific, one might want to approach some ingredients with types of limitations that you wouldn't

use for other ingredients. I believe that Bill Soller made that point, that this something where you look at individual ingredients and decide what limitations are the most appropriate, and I think you are quite properly making that point.

CHAIRMAN GENCO: It would seem that for these oral topically applied agents that Bill's point about concentration would have to be considered, so you may come into a whole new set of adverse effects with the higher concentration.

The other thing is, with a different formulation you may actually change the absorbability. Many of these agents are safe because they are not absorbed very well systemically. You may put something in a dentifrice, for example, which increases their absorption across the mucous membranes, and now you've got different absorption characteristics. So, I think that has to be looked at also.

So the safety issue isn't just straightforward maximum dose as if you took 1.7 mg and swallowed the whole thing once a day, it's concentration and also absorbability because even if you swallowed it, if it

wasn't absorbed, it would be excreted in the feces, unless you had something in there that made it absorbable through the mucous membranes.

MR. HUTT: Bob, I would only point out -- and I cannot speak for all of the Category I active ingredients -- but when we are dealing with the fixed combination of essential oils, these are food flavors, and they are contained in many of the foods that we eat every day, and that is why I suggested that one might look ingredient-by-ingredient because the concerns you just raised probably would not be relevant to this particular fixed combination.

CHAIRMAN GENCO: Okay. Max?

DR. LISTGARTEN: These four fixed ingredients, do they have to show up in the same ratio?

MR. HUTT: Yes. All of us have assumed that, and I'm sorry if we didn't make that clear, Max -- absolutely.

CHAIRMAN GENCO: Any further questions about what we've heard from Bruce, Peter of Mike with respect to the Warner-Lambert fixed, and Bill Soller. We've had general principles, unique aspects of the fixed

combination.

Okay. I wonder if we could have now -- I think P&G presented us with a little different view. If we could have that discussion, then I think we could go to the individual products. Does somebody from P&G want to summarize their presentation or, Bill, do you want to address the questions that you posed? Yes.

MR. DOYLE: I'm Matt Doyle. I'm the Associate Director and Senior Researcher for Proctor and Gamble Research and Product Development Worldwide. We have provided you with direct answers to the specific questions that Dr. Bowen had provided us, and didn't want to add much beyond that.

What I thought I'd do at the outset, though, would be in a helpful way to reacquaint you or refresh your memory with how we chose to approach the whole issue around performance testing. Since we've done this with you now piecemeal over the better part of the last 18 months, you've had composites of data that we've submitted to you, and so I just kind of wanted to bring it together. Clearly, we did that in the submission you have before you.

We've taken a very principle-based approach to profile testing. There really are fundamentally two components to profile testing in our minds, and both are absolutely essential. The first involves establishing chemical availability of the active ingredient, and the second involves establishing biological effectiveness.

We assess chemical availability using standardized, well controlled analytical measurements on specifically things such as soluble fluoride, soluble stannous -- you heard about these earlier -- and we use DRA to do this for CPC to test biological effectiveness via plaque glycolysis and regrowth. Importantly, this is an in vivo method which evaluates an active ingredient under natural salivary dilution, plaque uptake, retention, and clearance conditions in the oral cavity. So this is a rugged, rough road test of what's going on in vivo.

It involves asking a small base size of subjects to abstain from oral hygiene overnight. So we're not asking these individuals for extensive lengths or periods of time without oral hygiene. This is possible due to the lower variances associated with the

fact that we're making kinetic measurements, not point observations. So there's naturally some statistical power in that type of an approach.

We have provided data in our submission showing how specific common excipients and changes therein in product formulations affect both chemical availability and biological effectiveness. We have correlated these observations with clinical effectiveness. Said differently, we and others have tested both effective and ineffective formulas clinically.

Net-net, in our experience, this combination of performance testing adequately discriminates product effectiveness. That's all I wanted to say right now. Myself and my colleagues would be more than happy to address any questions you have.

CHAIRMAN GENCO: I think what you have presented is a very different approach for the in vivo, anyway, that is, we're hearing about a two-week experimental gingivitis which gets to the issue of gingivitis, apparently validated against a six-month gingivitis effect. The question to you is, is your

plaque glycolysis and regrowth, in your mind, sufficiently validated against a six-month gingivitis effect?

MR. DOYLE: Yes, we believe it is. It has adequately discriminated, in our hands for the better part of a decade, effective and noneffective clinical formulations.

CHAIRMAN GENCO: Is there anything unique to your agents which would argue to use that, the plaque glycolysis and regrowth, versus, let's say, a two-week gingivitis as the performance standard?

MR. DOYLE: Yes. We are not trying to place one above or in context of the other. Clearly, we haven't tested our active ingredients under an "experimental" gingivitis approach or model, series of models, so I can't provide you with data there. All I can address is clearly what we have done with our active ingredients in a PGRM context.

CHAIRMAN GENCO: But you did mention that maybe a gingivitis model might be appropriate in your presentation?

MR. DOYLE: In the submissions?

CHAIRMAN GENCO: In your submissions.

MR. DOYLE: That would be clearly one place we would encourage people to look at or think about, though we cannot stand here before you and say that that would be adequate for our active ingredients. We do not have data to support that.

CHAIRMAN GENCO: Is there anything about your active ingredients that would make you think it wouldn't be adequate, that it would be misleading to do a two-week gingivitis trial as a performance standard to predict a six-month gingivitis effect?

MR. DOYLE: Not proforma, though we are not clearly aware of what the statistical requirements for that kind of -- and you've discussed that among yourselves quite articulately, I believe. I think several of you are hitting at the heart of a very important matter there in terms of sizing, adequate sizing to break, and whether you're trying to get at significance vs. equivalence.

CHAIRMAN GENCO: I guess I'm asking another question. Is there something intrinsically different either about stannous fluoride or about CPC that would

give you misleading results if you did a two-week clinical experiment on gingivitis that would not be predictive of six-month gingivitis that you are --

MR. DOYLE: I can't rule that out at this point. I do not have data that say that would not be the case.

CHAIRMAN GENCO: Any theoretical --

MR. DOYLE: Just from a mechanistic standpoint, I'd bring you back that these things work by different mechanisms, and that may influence their overall performance in an EG kind of model.

CHAIRMAN GENCO: You've done some experimental gingivitis experiments, that these agents work on experimental gingivitis.

MR. DOYLE: We have not carried out experimental gingivitis kind of testing with these specific formulas.

CHAIRMAN GENCO: Your short-term spontaneous gingivitis then? I remember some short-term studies, 30-day studies. I guess I'm getting at can we be fooled if that was a performance standard for these agents, too, that is, a two-week gingivitis, would we be misled?

MR. WHITE: Donald White, Proctor and Gamble. There's obviously different types of EG models. There have been published studies on experimental gingivitis for stabilized stannous fluoride formulations which have shown efficacy, and there have been published studies, as I understand it, in the literature for materials like CPC which, again, have shown efficacy. I guess I retranslate the question -- there's a difference between can an EG show efficacy for these ingredients, and I think it can because that's been published.

That's a separate question from, does that mean it's a good profile test because a good profile test, there's more to it than just can it show an effect related to the biological effect? Is it reproducible? Is there statistical requirements for the testing straightforward? What kind of test do you need to carry out in order to establish efficacy? And so there's more to, I guess, defining what a good profile test is than the fact that it can show efficacy in one biological model, let's say, versus another.

So, yes, they've shown efficacy. If we applied them as profile test for our products? No,

because we've been successful at applying the test that you see. See, this is sometimes a difficult point for you folks perhaps on the panel because how these tests evolve? These tests are not picked a priori. These tests usually evolve during the development of the product and the ingredient in the formulation. And so, consequently, as you are going into clinical tests, you try to run screening assays to show whether or not your formula is going to have activity, picking the right dosage, and so on and so forth. And then as you have success in your clinical trials, those types of profile studies end up becoming the assays that you use to qualify variations in the formulation.

So, when you come to us and say, have you tested this in different types of assays? Well, of course, we haven't gone to certain types of assays if we've been successful with the ones that have evolved in the development of the product and the proof of clinical efficacy for the active ingredient.

CHAIRMAN GENCO: Okay. Thank you. You've answered my question. Max.

DR. LISTGARTEN: I think you've made the point

very clearly that the mechanism of action is going to determine eventually what kind of a quick assay one is going to use, and if you're dealing with fluorides I can see where a type of assay that looks like glycolysis makes a great deal of sense, but it doesn't necessarily -- it's not necessarily useful for essential oils, for example. So, I think any attempt at trying to find a standard way of assaying different products is doomed to failure. I think you more or less have to develop quick assays which a particular manufacturer uses for a particular product because it works in a certain way and it may not be applicable to anything else. So we're going to be stuck with a whole range of different ways of assaying different types of products. Now, how we go about putting this in a monograph, I'm not sure, but it's going to be very difficult to have "a" standard assay for a whole bunch of products.

CHAIRMAN GENCO: Bill?

DR. BOWEN: As you know, I had several comments on your original submission, and I have to admit a considerable number of them you have answered, but I'd be remiss to leave you with the impression that

I was totally satisfied.

(Laughter.)

MR. WHITE: That's not surprising.

DR. BOWEN: The first concern I still have is that we, on the panel, as I indicated, went to great lengths to point out that a plaque claim is a clinical claim and, therefore, you need to show some effect on gingivitis. And, in fact, I'm still a little concerned that you're not proposing to deal with gingivitis, and you have partially allayed my fears, but not totally, and I'd like to hear a little more elaboration on that.

The second problem that I have that I don't think you answered completely, and that is in the plaque glycolysis regrowth model -- and, conceptually, I like it because you are showing some activity that I would really like to see, that I can relate to -- but I look at the data and I see that you can't distinguish between -- statistically, that is -- between CPC at a concentration of 0.018 percent, 0.019, 0.027, and 0.038, which is the concentration that you propose to use in your formulation. So, therefore, somebody could have something that's lower than that and you're not going to

be able to distinguish it. So correct me if I'm wrong.

MR. WHITE: I'll let Matt answer part of the question about the PGRM, however, if they were below .038 in a DRA assay, they would de facto fail the profile. The would have already failed the profile. We have a lot of experience with this with caries. There are sort of a hierarchy of tests, and the first test shows is it chemically there. Then you run, in the case of CPC, a DRA assay because you say, okay, can it bind to an anionic substrate? And then if the answer is yes, it binds to an anionic substrate, at least equivalent to the lowest available dose that clinically worked, then you go to the next test which is does it show confirmatory biological activity in plaque? And if the answer to that test is yes, I'm not so worried that it statistically split from .025 percent CPC because that would have failed the prior test anyway.

DR. BOWEN: How specific are the filters? Do you -- there isn't any description on the filters. Are these standardized filters that can't be changed or have a high reproducibility?

MR. DOYLE: We have been working with them for

the better part of ten years now and have not seen variances associated with assay performance conditions. We run check samples inter- and intra-assay and have not seen that. So I can only answer your questions to that degree.

Within the context of our quality control program, we've not seen anything that would affect an outcome.

DR. BOWEN: And you were going to answer the problem I have with the no gingivitis study.

MR. WHITE: I was going to try to answer it. Well, the key here becomes -- when we think about profile tests at least for caries, Bill, you think about four things. Can a profile -- you're sort of trying to decide here whether you need to run -- is an EG going to give you something better than what you're getting with, let's say, a PGRM? So you're asking which test would be more preferable, and there are a number of factors that could go into choosing whether a test is enough, I guess, to use a word.

The first thing, a test has to show activity for clinical formulas; the second, that it has to

clearly distinguish those from the placebo controls that you had in your control clinical trial; the third is that you have -- now it starts to get trickier -- you have to have some activity by a mechanism of action which is reasonably associated, it seems to us, with clinical activity. An example in caries would be fluoride uptake. There may not be a linear correlation, but there's some correlation between uptake and activity. And then, lastly, it's helpful to know how control formulations vary as a function of the statistics of the model -- that is, again, back to our point, is a model usable as a profile, if there is so much variation in a type of test that it makes it difficult to compare to control formulas, then even though it might be biologically good, it might be a lousy assay to compare formulas in.

Now, in a lot of cases, the mechanism of action isn't completely known, and so your surrogate has to measure enough of it that you can be confident that you still have activity. And one of the things we like to use is, can it predict when a formulation should fail? In the case of CPC, we know that because we have

clinical formulas where when you add a surfactant to the activated, there's actually clinical evidence that they are, in fact, less effective and, sure enough, we see less activity in the PGRM test.

In the case of stannous fluoride, we have data where we can actually deactivate the 10 fluoride portion of the formulation through increasing the pH, okay, and you precipitate out 10 fluoride. Still have people brush with the product in a normal PGRM assay and you'll see no activity for the formula. And I have that data with me here today if you want to see it, but that's an example of the kind of test to show, okay, if the formula is deactivated in a known way and that is predicted by the assay, then you have more confidence that the assay is predictive of what you would reasonably see in the clinic. And those are the kind of thought processes we go through in "validating" the model because you can't prove a negative. You don't know -- you're not completely confident that some excipient would never have some effect. I mean, you just simply don't know, but you have to come up with a series of tests that are reasonably predictive, and it's

extremely important to be able to predict when it would fail, when by chemical means or physical means you've changed a formula and you can, in fact, prove that it would fail in the assay and PGRM meets those criteria.

Now, what Matt said about EG is true. We do not have as much experience with EG, either statistically or experimentally with these things, so I can't really tell you. They were not used as part of the formulation development plan. These tests were used to place our clinical studies. So the clinical studies were placed on the basis of what we saw in the PGRM tests, and all we can really put forth to you is that we spent $.5-$1 million on each of these tests, and that was typically based upon what we had in these assays. So, if they fail, I guess I'm in trouble.

DR. BOWEN: I'm a little concerned about the 20-percent leeway that you're allowing. If you look at pH values around -- which, by the way, I'm not too happy with either because I don't think you get them low enough, but that's another day's discussion -- but if you've got 20 percent, say, of 5.5, now you're getting into an arena where they're probably not being

effective. Now, knock 20 percent off 5.5, and I think you're down to 4.95 -- am I right?

MR. WHITE: Yeah, but don't forget the pH's that you're measuring are in a buffer after the in vivo treated plaque has undergone a kinetic analysis. So it isn't the same as an in vivo pH of 4.5. They are not -- in a relative sense, they are similar, Bill, but in an absolute sense they are not. A PRGM pH of 5 isn't the same as a plaque fluid pH of 5 in situ. It's just not because the plaque sample which has been treated in vivo, the saliva has had a chance to clear out the active and so on and so forth. That plaque specimen is assayed, it's put into a buffer, and then it undergoes a kinetic analysis after it's standardized. That's a very difficult assay to pass because you're antimicrobial's been diluted. It's already been diluted out of the oral cavity, and now you've further diluted it into a sample buffer. So things have to be fairly active in order to maintain their accuracy.

DR. BOWEN: Twenty percent is a heck of a lot of acid. I mean, you could easily have tipped from no-effect to effect with a 20-percent variation.

MR. WHITE: The 20 percent, I think, is chosen on statistical grounds. I hear what you're saying. It's chosen on statistical grounds rather than on absolute grounds. But we wouldn't just be measuring pH, we'd also be measuring the clearance curve of activity, which is based upon pH, but it's the entire curve of activity as a function of time.

DR. BOWEN: Okay.

CHAIRMAN GENCO: Max?

DR. LISTGARTEN: As I listen to this, it sounds to me that most of these assays deal with caries, or am I --

MR. WHITE: No, these were developed specifically -- the general metabolic activity of overnight-grown plaques was easier assayed by glycolytic assessments, and we felt that stannous fluoride was generic enough in its activity, and that CPC was generic enough in its broad spectrum activity, that that activity could be used as a marker only. So we're not making the connection -- we're not making a connection that, okay, that's exactly what the mechanism of action for gingivitis prevention is, we're saying a marker that

you have affected enough bacteria in situ to inhibit plaque sufficiently that it would have a clinical effect is, in fact, that assay.

DR. LISTGARTEN: So what you're saying is if the bacteria are dead in a large mass of organisms, you won't get gingivitis?

MR. WHITE: Or if they are metabolically inhibited, yes, and the correlations come from the clinical formulas working vs. the controls, and the fact that when you deactivate it in a way where you know you would deactivate clinical efficacy, you see no efficacy in the assay, yes.

DR. LISTGARTEN: And your reference standard was what?

MR. WHITE: The clinical formula that you ran your six-month.

DR. LISTGARTEN: Did you have a clinical reference like gingivitis assay?

MR. WHITE: Yeah. Of course, that's established in the six-month clinical trials that you run, yes.

DR. LISTGARTEN: Okay. So it correlates with

gingivitis.

MR. WHITE: Yes. What you wish you had but you never do is a set of formulas that you purposefully ruin and then run clinical studies on because Proctor and Gamble won't let me run the trials, they are expensive and they are not going to work. But that would be perfect. All you have is that data by accident, so accidentally make a formula with surfactant in it, and then you see that it only prevents plaque and doesn't prevent gingivitis, and then you say, oh, my goodness, I can't formulate CPC with the surfactant in it because it's not going to be effective. You learn those kind of things by accident, but no one will ever fund a clinical study a priori where you deactivate it and then try to run a so-called validation trial to show that your assay predicts a negative clinical result because no one wants to generate a negative clinical result. Do you see what I mean? You just never have that data. You only have that data after the fact.

CHAIRMAN GENCO: Lew?

MR. CANCRO: If we go back to the broadest principles that Dr. Soller introduced this morning --

availability, activity, concentration -- you're looking at three Category I ingredients that really function very differently. The essential oils must be delivered to penetrate the biomass and the manufacturer has proposed ways to do that, coupled with a profile testing -- physical, et cetera.

In this situation, the centers of activity of these two molecules are well understood. If the stannous ion is oxidized, if the pH is wrong, if the reserve stannous ion isn't there, then the outcome of loss of activity is very predictable. Stannous goes to static, it doesn't work. With cetopenidirium (phonetic) chloride, you're looking at the positive charge on the molecule which traditionally has been associated with its activity and, again, the manufacturer for each of those ingredients has provided both physical, chemical profile tests, tests which concern the centers of chemical activity of the molecules, and additionally are providing you with a biological test.

So, I think from the perspective of reasonable assurance, they've fulfilled those obligations of being able to modify these formulations and predict the

outcome.

CHAIRMAN GENCO: I think the question wasn't with the in vitro assays, but with the in vivo assay, and the essence of the problem is that we're asked to take a surrogate plaque reduction or regrowth reduction that glycolysis is really, I think, several steps from reality may have more to do with caries, but the plaque regrowth is what we're asked to look at as a surrogate for six-month gingivitis effect, and that is contrasted with a two-week experimental gingivitis which is a surrogate for six-month gingivitis effect. I think that's the essence, in my mind, of the dilemma.

MR. WHITE: Although you're implying that you would be more predictive in an EG. You may or you may not.

CHAIRMAN GENCO: But we've seen a lot of agents that have antiplaque effect but no antigingivitis effect.

MR. WHITE: Right, but those agents -- we're talking about an agent that's already been tested in a clinical gingivitis study of six months duration, and proven efficacy, and we're using that as a generic

control for metabolic activity on plaque. Again, these things are being used as markers, just like fluoride uptake. People have suggested in situ studies of fluoride uptake as a possible substitute for animal caries studies. There it's the same type of thing, they are saying that the in vivo activity of fluoride and being taken up into a tooth is a sufficient in vivo marker of activity that it can substitute for an animal caries. And I know people have entertained that notion. Now, there are people that disagree that that's applicable, but I'm just saying it's a similar type of thing.

CHAIRMAN GENCO: Well, it's certainly not simple.

Why don't we proceed. I have a suggestion -- unless there are more questions of P&G people. I have a suggestion. Let's take the fixed combination and answer the questions that FDA has posed to us, and then we'll go through the CPC and then stannous fluoride, and see if we can come to some resolution of performance standards, if necessary. Is that a reasonable way to proceed? We'll go back to the fixed combination. Okay.

The first question, is final formulation testing needed to assure the effectiveness of OTC antiplaque/antigingivitis product as a mouthrinse? This is really what we're talking about right now, is the mouthrinse.

Now, if somebody else wants to make a mouthrinse with the same four agents, what is -- is some final formula testing necessary to assure the effectiveness of that new formulation? Anybody disagree that it is necessary?

(No response.)

So the answer would be yes. Okay.

Are there any surrogate tests that could be used in lieu of the six-month gold standard clinical trial, to demonstrate antiplaque/antigingivitis effectiveness of the final formulated products? Now, we have been presented with in vitro and in vivo. Any comments here? Are there surrogate tests?

DR. LISTGARTEN: Well, Warner-Lambert seems to favor having both in vitro as well as an in vivo study, and I don't see any reason to go with anything different than what the company proposes. They seem to propose a

reasonable set of criteria which include both in vivo and a clinical trial.

CHAIRMAN GENCO: Anybody disagree with that? Pretty much as outlined, but maybe not in detail. You might want to revise those, less specificity as we had discussion?

DR. LISTGARTEN: But essentially with the same proposed portions.

CHAIRMAN GENCO: Proposal but maybe revising the statistics, revising the organisms, et cetera, that sort of thing.

DR. LISTGARTEN: What do you mean by revising the statistics?

CHAIRMAN GENCO: Well, they require the .25 log reduction.

DR. LISTGARTEN: I'll defer to Ralph.

DR. D'AGOSTINO: I think yes to your question, revise in the sense that this is an example of it. I think that the company, whatever company it be, has to produce evidence that, in fact, they have a validated procedure. And then they have to justify what they mean by equivalency. They have to justify what they mean by

all the different steps in the trial, but I think the protocol is a nice example for them to point to and for our deliberation.

CHAIRMAN GENCO: So it would be a wording revision, appropriate statistical analysis, for example, rather than prescriptive, this absolutely must be the way you do it. And, similarly, for the in vitro, appropriate organisms representative of the flora in gingivitis, for example. Okay. So those are two revisions that we could look at the detailed protocols that were given and make such revisions. Okay. Bill?

DR. BOWEN: I'd like to see some specification on how much leeway there is from the proven product. I'm not comfortable in leaving that open. I don't have an amount in mind, but I think it should be specified, but I don't think necessarily to tell them how the statistics are to be done or anything else. But I'm not comfortable leaving it open.

CHAIRMAN GENCO: I have a suggestion. Do you want to take a crack at the wording of that? Maybe you and Ralph could do that -- that is, in the in vivo experiment on gingivitis, to look at the statistics

paragraph and revise that so that you're happy with it, and maybe we could look at that again. And with respect to the bacteria, Max, do you want to take a crack at that in the in vitro?

DR. D'AGOSTINO: What's the problem, the 10 percent?

DR. BOWEN: Well, they have proposed 10 percent, and personally I find that acceptable.

DR. D'AGOSTINO: But they propose 10 percent in such a way that the new formulation could be 10 percent worse than the old formulation, and they would say that the new formulation is all right. I mean, the statistics right now allows them to say equivalence, if they are 10 percent worse than the old formulation.

DR. BOWEN: Do you feel it should not be allowed to be 10 percent worse?

DR. D'AGOSTINO: No, I'm just thinking that for us to pick the 10 percent or for us to pick the direction is something that is a discussion with the FDA that would be better left with the FDA. We think that there's a range -- we don't want to get trapped into the thing that Max was raising, that we don't want to force

them into equivalence where then they would have to run monster sized tests, but at the same time I don't think that we necessarily have to say 10 percent is the magic number. I think that that's a discussion item that they could have with the FDA and make a justification for as opposed to us saying that 10 percent is the magic number.

CHAIRMAN GENCO: Would it be appropriate to do that and then maybe report back tomorrow on something -- maybe at breakfast you could discuss, or this evening, Bill and Ralph? Anybody else want to get involved in the statistical redrafting? Max, would maybe you and Gene look at the organism, I think that was the other point of contention, in the in vitro. Is that list of organisms -- are we happy with that, or should we be a little more general?

DR. LISTGARTEN: I would like to be more general. I think I would like to leave it up --

CHAIRMAN GENCO: Maybe you could draft some appropriate wording, and I think Ralph's suggestion of for example -- I mean, you may use the list, but use it as a for example. Okay.

Was there anything else that anybody -- any other problem with the two protocols that were presented? If you were taking direction from Warner-Lambert but with some modification of the two protocols, the in vitro and the in vivo, for their product?

MR. CANCRO: Only to reinforce the point for example, because there are many modifications of these tests, as you well know.

CHAIRMAN GENCO: Okay. Now, Chris?

DR. WU: I have a question about an initial inoculum concentration. I did talk to Pauline and it was not in the protocol. I think it should be specified that the initial test bacterial concentration used like OD1 or whatever should be more than 10_8 cells per ml. The quantity of cells were not specified, but she said it was not in the protocol. It should be.

DR. PENN: Dr. Wu, in the protocol, there is a generic statement that says inoculum should be adjusted to the nearest whole number. We would be -- we would proposed, and we are in entire agreement, I think the industry would favor this as well, to set the inoculum of all of the organisms at a 1 percent

transmission. I think that would be a reasonable number.

CHAIRMAN GENCO: Is this what you are suggesting? Do you want to then make that revision and bring it back to us tomorrow morning? Okay.

So three revisions so far. One on the types of organisms or the species, another on the inoculum for the in vitro, and the statistics for the in vivo.

Lew, did you have other areas where you would want to make it more general and use that phraseology?

MR. CANCRO: No, but taking Ralph's point, how much of a difference is going to be acceptable -- you know, that becomes an interesting question. It's unlikely that in a study you're going to get two numbers that are identical. That's going to be a pretty rare phenomenon. But I would kind of remind you that under good manufacturing practices, these formulations can vary up to 10 percent. I mean, not by design, but by --

CHAIRMAN GENCO: It's allowable, and has no biologic consequence.

MR. CANCRO: Exactly. So that if you take that where you're actually starting with a difference

which could be up to 10 percent and then clearly the magnitude of the clinical effect must certainly have some resemblance to that -- I mean, I don't know what it would be, but --

CHAIRMAN GENCO: Well, I think Ralph and Bill can craft some words that would accommodate that.

Okay. With respect to the other -- the fourth question, any general recommendations on final formulation, do we take that to mean that other dosages -- I mean, where are we going to deal with the issue of dosages and dosage forms? Can we deal with that here? What did you have in mind here for No. 4?

MR. CANCRO: That should be done now.

CHAIRMAN GENCO: Okay. So let's take No. 4 to mean general recommendations on alternate dosages and dosage forms, the discussion we had in midafternoon. Now, the proposal from Warner-Lambert -- and we're talking about their product, the fixed combination -- was that a six-month clinical trial be carried out, and we had extensive discussion that both safety and efficacy should be looked at in a six-month trial. I brought up the point, isn't a three-week gingivitis

trial sufficient, and I think we had that discussion. What are your feelings? The six-month trial for a dentifrice, for a gum, for a floss, what have you, with gingivitis as the outcome and safety, adverse effects?

DR. BOWEN: I would support that.

CHAIRMAN GENCO: Single, or two?

DR. BOWEN: Single test.

DR. McGUIRE-RIGGS: One six-month.

CHAIRMAN GENCO: Any objection to that?

(No response.)

Okay. Bob, is it appropriate to take a vote at this point, or if we have a consensus --

MS. KATZ: At this point, if you have consensus, you really don't need to take a vote, but we'd also like to engage in other -- if there's anything else that would come up, or other issues related, this is the time to do it now.

CHAIRMAN GENCO: Okay. So we don't know with the efficacy/safety issue of new dosage formulations, what about the dosage issue? So the efficacy/safety is a six-month trial, adverse effects and efficacy, gingivitis.

Now, what about the dosage? Remember the issue there was the total dose, if totally swallowed, was 51.7 mg. Is that the maximum dosage regardless of concentration, regardless of absorption, et cetera? Bill, do you want to make some suggestions here?

DR. BOWEN: I don't know about the potential toxicity of the essential oils. Peter makes the point that these agents are used extensively in food products as flavoring and so on, and that gets me -- rather than assuage my fears, makes me more concerned because now I'm getting worried about the total body burden. And given that we know there are larger volumes of toothpaste swallowed than there are, say, of mouthrinses, I'm getting concerned about when do we get into toxicity? Are these products so totally free of toxicity that we don't have to be concerned? And, frankly, I don't know the answer to the question.

My gut feeling -- no pun intended -- tells me that we probably could go with the maximum dose on exposure of 51, or maybe allow 10 percent or 15 percent more, but don't ask me to justify the rationale for that comment because I don't have any.

CHAIRMAN GENCO: Just to clarify, that's a single day -- single dose, single day, single administration.

DR. BOWEN: Well, it have to be. I assume it would be used twice, toothpaste would be used twice a day.

CHAIRMAN GENCO: Then it would be half that. The single dose we're talking about for the rinse is 51.7 mg a day, single rinse or two rinses, what is the dosage?

MR. HUTT: Twice a day, and just to clarify, Bill, the company was not suggesting anything in addition to the 51.7. GMP means it might go, on occasion, over the 51.7, but that would be a point upper limit, you know, plus-or-minus GMP.

Now, the lower limit that the company has recommended is the 80 percent figure.

CHAIRMAN GENCO: Okay. So the suggestion is the two times per day use, if you have a concentration in dentifrice or other formulation not to exceed 110 percent of the 51.7 mg per day.

MR. VINCENT: Jack Vincent, from Warner-

Lambert. The 51.7 mg is per dose of the mouthrinse. So it would be 51.7 mg delivered twice a day. And so it would be the same for the mouthrinse, the calculation.

CHAIRMAN GENCO: Or any other formulation. In other words --

MR. VINCENT: That's correct.

CHAIRMAN GENCO: -- it's a total -- and if it was a chewing gum, we might have to say something like 103.4 -- 100 mg a day, something like that, total.

MR. VINCENT: Correct. But I just wanted to make clear that it is 51.7 mg per rinse dose, so it would be delivered twice daily.

CHAIRMAN GENCO: What would be the most effective way of expressing this, daily dose then of 100 mg, because if it's a gum or a floss, it might be multiple times per day.

DR. BOWEN: But is the term "dose" really correct? If you have it in a chewing gum, the chances are you're going to swallow the whole lot. With a mouthrinse, you probably won't swallow more than maybe 1 or 2 percent, and with toothpaste you can probably see some people that will swallow as much as 10 or 15

percent. And I'm not sure dose is the correct terminology. To me, it implies a systemic intake, and we're not really talking about a systemic intake here.

Now, having said all that, I can't come up with the right term either.

CHAIRMAN GENCO: I'd like to suggest that we consider that over the next couple of hours, just as you are considering some of your issues, and that we return tomorrow morning with a proposal for you. I think the important issue is the concept, Bill, that if we could agree on the concept of this upper end and the range, then we can work this evening and see if we can arrive at a more detailed approach to this. Bill

DR. SOLLER: I was just reacting, Bob, to something that you said about adding that 10 percent and, generally, while there may be ranges in monographs that would be the effective range for the product, that percentage is usually reflected in the USP monograph from a technical manufacturing spec, so I would leave that out of your consideration.

CHAIRMAN GENCO: So that's the range that you would expect chemically in these preparations.

DR. SOLLER: Well, you are allowed to have some range, for example, 95 through 105 for aspirin, but it's a 325 mg dose, for example. You could say the same argument for 1 percent hydrocortisone, and it's to account for stability, shelf-life, et cetera.

CHAIRMAN GENCO: So we'll talk about a dose which is in the range of twice 51.7, adjusted for ingestion, so we'll get a reading on that tomorrow morning. Lew?

MR. CANCRO: Bob, I think, at least from my perspective, the dose is what is applied at any one time. The exposure level, the maximum daily exposure level, is really the 102 or whatever that adds up to. So that's the figure that --

CHAIRMAN GENCO: So that's what we want tomorrow, some guidance on the maximum daily exposure.

MR. HUTT: We will provide that.

CHAIRMAN GENCO: Okay. Any other general recommendations with respect to this fixed combination product?

(No response.)

Okay, fine. Let's proceed now to CPC. Let's

go through the four questions. First, is the final formulation testing needed to assure effectiveness of an OTC antigingivitis product? We're talking about a mouthrinse like the existing CPC that's been tested. Someone wants to duplicate it. Is there final formulation testing necessary? Anybody believe it is not necessary?

(No response.)

So it is necessary.

Secondly, are there surrogate tests now that can be used in lieu of the full-blown standard six-month, gold standard, antiplaque/antigingivitis for testing effectiveness of the final formulated product? Again, we are presented with an in vitro and an in situ/in vivo test. Do we believe these are adequate surrogates for the six-month antigingivitis, or is there another surrogate? Somebody want to get the discussion going? Let's take the in vitro, the DRA, first.

DR. BOWEN: The DRA certainly show the availability and, as Matt and Don pointed out, the DRA on its own provides part of the information that's needed, and then that in combination with the plaque

glycolysis and regrowth I think were based on the data that they have provided supporting information that they have an effective formulation.

I think it's important to point out that one or the other, on its own, isn't sufficient.

CHAIRMAN GENCO: So you think that both of them in combination represent a good surrogate battery for CPC?

DR. BOWEN: And, again, in combination with antimicrobial testing as they've outlined. Again, I have some problems with some of the details, but basically the approach is okay.

CHAIRMAN GENCO: So antimicrobial and DRA in vitro and the plaque glycolysis/regrowth in vivo, in tandem, in combination. Okay. That's the proposal. Lew?

MR. CANCRO: I think that adequately defines the chemical basis of activity and availability. I would agree with Bill.

CHAIRMAN GENCO: Max? Anybody object to that?

(No response.)

Any revisions to what they propose, what P&G

has proposed on any of those tests?

DR. BOWEN: Well, again, originally there was no defined specification of type of subjects and the conditions weren't clearly enunciated and in the response they were, so I feel comfortable now with the selection of patients and the exclusion and inclusion criteria.

CHAIRMAN GENCO: What about the antimicrobial test, would you suggest any revisions?

DR. BOWEN: Well, the revisions that I suggested are not likely to be accepted because I like to have -- include saliva in a lot of these tests, and saliva is difficult to handle so people don't like to use it. But the tests at the moment, I think most people in industry recognize their shortcomings because they are not biofilms, and whether there's an adequate in vitro biofilm to test some of these products is debatable, but certainly it's not well established. So I would think we have to go along with what's available, and hopefully these monographs are not set in stone.

CHAIRMAN GENCO: So the rationale is that is the formulation inactivating your testing for biologic

activity, relevance to the clinical situation is another issue.

DR. BOWEN: Right.

CHAIRMAN GENCO: Okay. So we've answered No. 3 also. Is everybody comfortable with that? The battery of three -- antimicrobial, DRA which is absorption release, and then PRSG which is the plaque regrowth and glycolysis -- pretty much as recommended by Proctor and Gamble.

(No response.)

Okay. What about No. 4, the issue of new formulations, the dentifrice, the chewing gum, the floss, what have you, is that same battery adequate, or is something else needed? Now, I know that P&G didn't address that, but can we be instructed by what we've discussed with respect to Listerine? Is this going to require a six-month clinical trial, a single trial, double trial, safety and efficacy assessment?

DR. BOWEN: I would be very concerned about toothpaste having 10 times the amount of CPC in it that a mouthwash does. I suspect, based on what I read on the toxicity, that the likelihood of disclamation is

very high. I don't know how P&G feels about it.

CHAIRMAN GENCO: Do you want to make a comment?

MR. DOYLE: I just think within the context of whatever this other formulation is, that there are going to be questions, natural questions that come out in terms of safety and it would be prudent for people to test those. So our position would be we would likely accept some sort of clinical test. I don't know whether it would be six months in duration, but clearly that would be a prudent approach.

CHAIRMAN GENCO: And in that test, Bill's point is that if the principle of 8 to 10 times higher concentration was used in a dentifrice, that you'd be happy with that, looking in the six-month clinical trial for adverse effects as a measure of Bill's concern?

MR. DOYLE: Yes. I don't think a six-month trial is necessary, but I think some sort of clinical test is certainly a prudent approach to the whole thing. Just because you've got 10 times the concentration of drug there, if that's not bioavailable and it's all tied up by surfactants in, let's say, a CPC dentifrice, then

you're going to have a mitigated safety concern as well. You're just not going to see the same level of disclamation in a dentifrice even though you've got 10 times as much. That said, I still think it's a smart thing to do to test this thing on in vivo clinically this new dosage form, whatever it would be, whether chewing gum, sprays -- you know, your imagination can run wild here.

CHAIRMAN GENCO: In terms of the final submission to the FDA or final test of this new formulation or new type of delivery, the six-month clinical trial may not be unreasonable. I mean, in the development in the company you may do various things up to that -- shorter trials, et cetera.

MR. DOYLE: Yes, I agree with that.

CHAIRMAN GENCO: But that's not what we're dealing with, we're dealing with the final issue of is this effective, and can a claim for antigingivitis effect of this dentifrice be made, and safety?

MR. DOYLE: That's correct.

CHAIRMAN GENCO: Okay.

DR. McGUIRE-RIGGS: Do we want to put some

interval point in that six-month clinical trial in addition to just the six-month endpoint, to catch some of these adverse reactions?

CHAIRMAN GENCO: I think that it's already built in. We're talking about the traditional trial as a three-month --

MR. CANCRO: I think Bill Bowen has raised the appropriate issues -- the higher concentration, does it disclamate the cells of the mouth, is it irritating, et cetera. So the manufacturer has the burden not only of showing the effectiveness of the new dosage form in some manner satisfactory to you, but also in demonstrating that these other concerns can be dismissed.

CHAIRMAN GENCO: So the adverse effects would be looked at continuously monitored through the trial, this is what you're thinking, and it might happen in the first week or two.

DR. McGUIRE-RIGGS: But do we need to formally state that question.

CHAIRMAN GENCO: I think we could. We could certainly suggest that the six-month clinical trial have adverse effects continuously monitored, or frequently

monitored.

Now, what about the dosage? Are we agreed that the six-month clinical trial for the new formulation, new application is reasonable? Any objection to that?

(No response.)

All right. What about the dosage? Bill, do you want to make some suggestion that five-fold dose be tolerated, or the maximum drug exposure, daily exposure, be something less than the multiple or the exact multiple of the two times per day CPC mouthrinse?

DR. BOWEN: I would make that suggestion, and that --

CHAIRMAN GENCO: Comparable to?

DR. BOWEN: I'm trying to do the math here.

CHAIRMAN GENCO: Yeah, it's 0.38, isn't it, percent?

DR. BOWEN: Yes.

CHAIRMAN GENCO: So it's the dose comparable to .038 percent used twice a day exposure in 20 ml. So the maximum daily exposure be equal to but not exceed 2 times .038 percent in 20 ml. I'm sure someone from P&G

has that figure, but we could --

DR. SAVITT: Just a point of clarification. Wouldn't this sort of issue be covered in the safety specifications, or shouldn't it be covered in the safety specifications as they are laid out?

CHAIRMAN GENCO: Yes, but we are talking about a new formulation. We're not talking about -- we're talking about dentifrice or released in a mouthguard or something else.

DR. SAVITT: In laying out safety specifications for any product, whether it be CPC or any of the things we've looked at, there's a maximum that seems permissible -- for instance, with hydrogen peroxide, while a 1.5 percent or 3 percent may be perfectly okay, you don't want them going up to 30 percent simply because they want --

CHAIRMAN GENCO: You're talking about the concentration now.

DR. SAVITT: The concentration, that's correct.

CHAIRMAN GENCO: So we have two issues. One is the daily maximum exposure, total amount, and the

other is the maximum concentration.

DR. SAVITT: Should these figures be incorporated into the safety section of the particular product in the monograph.

CHAIRMAN GENCO: Yes. We have some data maybe on the maximum daily exposure, but we don't have data on concentration as we do with hydrogen peroxide, I don't think.

MS. KATZ: That was the point that I was going to make, and I was going to wait until the end of the discussion to come back a little bit. Un terms of listening to some of the discussion about dosage forms and safety for doses and I'm getting a little concerned because we're kind of going a little bit too far afield, kind of extrapolating into things that don't exist. And it's basically -- the way we've dealt with it in the past with other monographs is sort of to use a very general term, like to say traditional dosage form, and that will cover those dosage forms that are considered traditional. It also kind of puts a -- curtails us from creating things that don't exist like, for example, aerosols or other kinds of spray containers which may

have other regulatory problems, and so therefore that's not an area we want to tread on; from going into areas of devices which have different regulatory standards and create a combination for a drug and device; that I think maybe just to bring it back in terms of thinking of things that we don't want to necessarily limit it to a gel particularly, or a lotion, but to say that a traditional dosage form might be acceptable, might be the better way to kind of approach the discussion.

Also in terms of when we're thinking of dosage limits both for concentrations and for the allowable daily doses, what in the past was done is we've gone back to the manufacturers to ask them to provide a good deal of that data to us, and then to see if that seems reasonable to the committee itself because part of the concern that I also have is that I don't want us here to be extrapolating to doses beyond what is a safe and reasonable limit because some of the products that we may be talking about may have a narrow therapeutic window and we don't want to go beyond that.

So these are things that should sort of play into the discussion and, again, when we're asking some

of these questions, we're asking for the general advice so that we can use the advice in terms of trying to write what our recommendations would be that we may not necessarily say expect hard and fast numbers.

CHAIRMAN GENCO: Okay. With this series of products, though, one of the very first traditional ways of applying it is in a dentifrice, unless you're recommending we just stick with mouthrinses and maybe gels as a variant of a mouthrinse.

MS. KATZ: No, no, no, I was just using that as an example so that if you want to talk about dentifrice in general, that's fine, but I guess where I was concerned where I hear things about nontraditional types of problems, and I don't want us to start treading that water because in the past when nontraditional forms have come in, they usually do come in under a NDA as opposed to coming through the monograph.

CHAIRMAN GENCO: So our discussion really is mouthrinse and dentifrices, and where we're dealing with alternate formulation is really the dentifrice.

DR. McGUIRE-RIGGS: But where do gels that are in mouthguards fall in that category?

MS. KATZ: That's correct. A gel could be -- if you feel that a gel would be a traditional form, that would be something that we would entertain as well because we are familiar with gels for other types of products so that it could be considered traditional.

CHAIRMAN GENCO: Okay. So --

MS. KATZ: If, in fact, you believe that it is traditional for these particular products for that use.

CHAIRMAN GENCO: Not for antigingivitis, but they've been used for caries.

MS. KATZ: Right.

MR. CANCRO: In a sense, you're trying to confine this creative session to liquids and semi-solids.

MS. KATZ: Exactly, things that we traditionally know about and use, and that it would seem that this would be appropriate, but I don't necessarily mean to curtail the discussion by saying that this has to be a mouthwash only for this particular product, if one feels that it may be extrapolatable to a semi-solid.

CHAIRMAN GENCO: So, from what I've heard then, both for the fixed product Listerine and for the

CPC is that the general principles of different formulations for liquids and semi-solid gels would be that a maximum daily exposure be comparable to the maximum daily exposure of the mouthrinse. That's what we're coming to.

MS. KATZ: Basically, but again there may be also -- and this the manufacturer would probably need to tell us, too -- if in changing the dosage form, that it changes what the availability would be of the particular product because in some cases it does change, and that that would need to be taken into account in the monograph itself.

CHAIRMAN GENCO: Okay. And how about the concentration issue?

MS. KATZ: That would be the same thing because in some cases concentration --

CHAIRMAN GENCO: We look for advice from the -- okay, so we won't get into that. But the issues have been brought up. Okay. Good.

Are there any other general recommendations for the CPC?

(No response.)

Okay. Let's discuss the stannous fluoride now. Nuance here, Bill Soller and P&G folks have pointed out that it may also be anticaries. Need we deal with that, or is that obvious? Do we just deal with the antigingivitis? Okay.

No. 1, do we need testing for the stannous fluoride if somebody comes up with a new preparation?

DR. BOWEN: Yes.

CHAIRMAN GENCO: Are there surrogate tests for the stannous fluoride containing antigingivitis preparation? Now, we've been presented with a DRA and the PRSG. Is that adequate -- and in vitro antimicrobial, or isn't that relevant here?

DR. BOWEN: The plaque glycolysis and regrowth model has been described and it's clear that it's an excellent method, the glycolysis part is certainly excellent for looking at the retention and activity of the stannous fluoride, and there's no doubt whatsoever that the inhibition of glycolysis is due to the presence of the stannous ion.

I'm a little less certain and I'd like to hear some more elaboration on the effect of the stannous

fluoride on the plaque regrowth because from what I read the stannous fluoride doesn't affect the deposition of bacteria during early plaque formation, and one could make the case that the stannous fluoride effect against gingivitis is not due to a bacteriocidal or antiadherence effect, but perhaps due to a fairly good astringent effect thereby reducing some inflammation and perhaps stopping bleeding.

CHAIRMAN GENCO: Somebody want to address that? We're talking about the PGRS as the surrogate, not the DRA, and it's interpretation. Do you want to address that?

MR. WHITE: Donald White, Proctor and Gamble. We routinely see the inhibition of plaque growth in a variety of assays, Bill -- in vivo assays, four-day nonbrushing models, so on and so forth. The issue comes to the fact, how is it that you can measure plaque regrowth in MPGM and say that it's important as a surrogate for clinical efficacy when you run clinical trials and you don't end up with a numerical reduction in plaque mass.

Over the years in our analysis of that, we

believe that data supports the fact that -- I think the reason we don't see reduction in the plaque mass is more related to artifacts of the stannous, not that it's not inhibiting plaque growth, mind you, but you end up with thicker films on the teeth, and that's part of the reason in those formulations you, in some formulations, you see some modicum of tooth stain, and in some individuals you see some tooth stain.

So, I think that's more of an artifact. That doesn't bother us as much, I guess, fundamentally in using the regrowth screen because I think -- isn't that where you're coming from? You're saying if it doesn't provide a numerical reduction in plaque in your clinical, then why are you measuring plaque regrowth in a PGRM? Well, it provides reductions in plaque regrowth and bacterial growth in most of our assays, it's just that once you get out six months there's quite a bit of tin in the film around the margin, and I think that ends up being graded as plaque, to tell you the truth. And we have some data to support that.

So that's the reason why we're fairly confident -- and we really do believe we should use the

regrowth and the glycolysis together because we -- although we haven't seen formulations that differ in their actions, we would be sensitive to the fact that we haven't prepared one -- you know, if we modified a formula, we'd still want to see effect for both. If we didn't have the PGRM regrowth, we would want to go to some other plaque -- a wire model or something like that, but in lieu of that, we use plaque regrowth in the PGRM.

DR. BOWEN: I think the glycolysis data is much more convincing than the plaque regrowth part of the model. Would you agree?

MR. WHITE: Convincing in terms of as a marker?

DR. BOWEN: Yes.

MR. WHITE: Well, if I knew exactly the mechanism of action, I guess I'd agree. But I'm measuring activity on plaque using a combination of assays, so I'm choosing regrowth in combination with glycolysis. For the improved anticaries activity relative to the old stannous fluoride, I agree 100 percent that glycolysis is definitely more predictive

there.

Incidentally, we're already running an additional in vivo assay because we run a rat caries. So the formula is being run in two in vivo assays. To qualify for the anticaries monograph, it's being run in an anticaries assay, and the improved version of stabilized stannous fluoride is usually more effective -- - is typically more effective than the original stannous fluoride toothpaste because the stannous fluoride is more available. So that's the first in vivo assay.

And then the second in vivo assay which we applied to the plaque/gingivitis activity is, in fact, the regrowth and glycolysis portion in PGRM.

CHAIRMAN GENCO: Are you satisfied?

DR. BOWEN: Yes.

CHAIRMAN GENCO: So what we're being asked, is there a surrogate test for the antigingivitis effect in the six-month clinical trial for stannous fluoride, and the answer is yes, from what I hear in the PGRM and particularly the glycolysis inhibition component. Is everybody comfortable with that?

What you're saying then is that you're going

to look at glycolysis in vivo as a surrogate for antigingivitis effect. Is everybody happy with that?

(No response.)

Okay. So somebody makes a new stannous fluoride preparation, they're going to have to do this PGRM, if FDA takes our advice, knowing that it doesn't inhibit plaque, there's no gingivitis endpoint here, and it's just glycolysis, but it's in vivo. Lew.

MR. CANCRO: And additionally, of course, the stannous ion, the company is going to do stannous ion.

CHAIRMAN GENCO: That's part of the -- from the USP.

DR. BOWEN: And the in vitro test on the effect of microorganisms.

CHAIRMAN GENCO: Okay. Also the in vivo antimicrobial effect or antiglycolysis effect.

DR. BOWEN: In vitro antibacterial.

CHAIRMAN GENCO: Okay. So two tests, the in vitro antibacterial and the PGRM. Is everybody comfortable with that?

(No response.)

Okay. Now, stannous fluoride in a different

formulation, anything different from what we've discussed for the others -- the six-month clinical trial both for safety and efficacy. Anything else?

(No response.)

How about maximum dose? Bill?

DR. BOWEN: It's already in a paste.

CHAIRMAN GENCO: Right. I'm thinking if they put it in some other formulation, a gel or what have you. That's what we're being asked to consider.

What about the maximum daily exposure, same principle, comparable to what is already given in the proven product. And the concentration, we'll take advice from the company, the FDA will take advice from the company relative to concentration if they change it to make it higher or whatever.

Any other general concerns on the stannous fluoride?

(No response.)

Okay. I think we've finished the agenda as set out for this afternoon. Is there anything else that we should discuss with respect to these issues of formulation?

MS. KATZ: The only specific issue is a logistic issue. Tomorrow's session is set aside for labeling and has been announced that way in the Federal Register. The third day, the way it was set aside was that there was extra time for whatever issues might be carried over. And it may be best to come back to address some of these issues on Friday morning, after we finish our regularly scheduled agenda, since it's a lighter day, rather than trying to push it in tomorrow.

CHAIRMAN GENCO: Okay. So what's hanging, what's left over then is the revision of the Listerine in vitro and in vivo studies, but the dosage which we also discussed, the company does not have to come back because they'll be responsive to the FDA's request for dosage direction.

MS. KATZ: Or if they want to, they can come back to give further discussion, if they want some input as well from the panel.

CHAIRMAN GENCO: And that will happen first thing Friday morning.

MS. KATZ: On Friday, right. I guess Rhonda would know this better again, since Friday was announced

for the specific time for the open public hearing. We could do it, I would imagine, after that.

CHAIRMAN GENCO: Sometime Friday morning. Okay. Is that clear?

MR. CANCRO: What is the status on the vote of appropriate combinations, will that occur on Friday?

DR. SHERMAN: Yes.

MR. CANCRO: Okay.

CHAIRMAN GENCO: Okay. Any other issues to be discussed? Any announcements?

(No response.)

I wonder if I could ask the panel just to stay for a few minutes, and thank you all, it was a very productive day, and we'll see you tomorrow morning.

(Whereupon, at 4:30 p.m., the meeting of the Dental Plaque Subcommittee was adjourned, to reconvene Thursday, May 28, 1998, at 8:30 a.m.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: MEETING

Before: DENTAL PLAQUE SUBCOMMITTEE

Date: MAY 27, 1998

Place: GAITHERSBURG, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.